Examining Sleeping Patterns and Quality of Life of Patients suffering from Parkinson Disease

Doctoral thesis

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Introduction

Demographic characteristics of the European Union evidence that illnesses affecting the aging population have a negative influence of national economic indicators. For the topic of my thesis I chose Parkinson's disease out of neurodegenerative diseases that affect mainly the aging population and negatively influences life quality.

By getting familiar with the Action programme of the European Union between 2010 – 2020 aiming to aid active aging interventions, the quality of life of Parkinson's disease patients got into the focus of my research.

In the course of my examination of quality of life and factors influencing that, I took special care to sleeping, activity, participation in social life, furthermore the possibility of patients with Parkinson's disease to drive a car who have Obstructive Sleep Apnoea Syndrome OSAS as an additional illness.

Definition of health quality of life

According to Section 1 of the Constitution of the World Health Organization (WHO) passed in 1946, "health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

Definition of Quality of life

My thesis examines the quality of life of Parkinson's disease patients, for this reason it is highly important to define quality of life and to examine its constituents. As it is defined by the WHO, "as individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment."

Generally, it can be stated that the measurement of "well-being" of an individual (or population, group of population) takes in consideration the subjective and objective dimensions along different physical and mental aspects important for them.

Objectives

1. The objective of my thesis is the complex interpretation of quality of life of Parkinson's disease patients, with special regard to problems arising from sleeping disorders and their solutions.
2. To call the attention to the importance of motor and non-motor symptoms of Parkinson's disease with the examination of quality of life and to raise awareness of their effects on the quality of life of the individual.
3. Psychological or social therapies appropriate to treat anxiety and depression have to be highlighted in the course of improving the quality of life of Parkinson's disease patients. These therapies are indispensable in order to maintain interpersonal relations, personal and social competences.
4. Sleeping disorders associated with Parkinson's disease may cause daily symptoms such as daytime sleepiness and mood disorder through night symptoms (insomnia, atony, violent movements during sleeping) and they can cause significant deterioration of quality of life, insomnia, REM behaviour disorder.
5. Justification of the importance of sleep examination in diagnosing Parkinson's disease at an early stage.
6. Highlighting the importance of proper medicinal treatment, adjusting and adequate medication to have an optimal effect of medicines and this way the delay of progress of Parkinson's disease.
7. How much the application of the Brussels law and the questionnaire developed by them affect the quality of life of Parkinson's disease and OSAS patients, their everyday lives, and to what extent does it change if they lose their driving licences.

Hypotheses:

1. I suppose that motor and non-motor symptoms prevent Parkinson's disease patients to a great extent to live their social roles and relationships.

2. I would like to find out whether treatment of cognitive disorders is less highlighted in relation to Parkinson's disease patients, which can make their quality of life even worse.

3. I assume that sleeping disorder appearing in early phase has a negative effect on the quality of life of Parkinson's disease patients.

4. In my view, the validation of the Brussels recommended questionnaire to be applied to monitor OSAS, facilitates the early diagnosis of sleep disorders, it is proper for further monitoring of populations with a great number of samples, therefore, in an indirect way it can contribute to diagnose the Parkinson's disease in early phase.

Scene of my researches.

I carried out my researches in Budapest, in the Sleep Diagnostic Laboratory at the Neurology Department of the Health Centre of the Hungarian Army. My research was led by Dr. habil Szakács Zoltán Ph.D. colonel doctor, neurologist, somnologist, head of department with a licence, president of the Hungarian Sleep Diagnostic and Therapeutic Society, member of the European Sleep Society, member of the American Sleep Society.

The basis of the research is the examination of Hungarian patients suffering from Parkinson's disease. At the same time, an alternative research is added to this basic research direction, the aim of which is to explore more thoroughly and understand the problems.

As far as we know, no in-depth research has been carried out in Hungary among Parkinson's disease patients in relation to quality of life, epidemiology, economy and sleep disorder.

Methods

The restriction of the population is crucial, as it is impossible to study the entire population of Parkinson's disease within the current material, personal and temporal limits, so there are some valid conclusions, but for a narrower social group.

Among the probability sampling procedures, multi-stage sampling was used by surveying patients with Parkinson's disease at the Sleeping Diagnostic and Therapeutic Laboratory of the Medical Centre of the Hungarian Defence Forces (Honvéd Hospital). In our research, we had a number of patients with Parkinson's disease at different stage and severity (stage 2 and stage 3 on the Hoehn-Yahr Scale,), diagnosed with disease earlier than the recent 5-10 years.
The quality of life of patients with Parkinson's disease was assessed using subjective (structured clinical questionnaires) and complex, subjective and objective (structured clinical questionnaires and polysomnography devices).

The quality of life of patients with Parkinson's disease was assessed using subjective (structured clinical questionnaires) and complex, subjective and objective (structured clinical questionnaires and polysomnography devices) research tools.

Polysomnographic data was analyzed by somnologists in accordance with the recommendations AASM, American Academy of Sleep Medicine.

Sleep Stages and the Apnea-Hypopnoe Index (AHI) were determined based on the recommendations of the American Sleeping Society and the American Academy of Sleep Medicine Task Force.
For determining correlations between the variables, Pearson correlation analyses and Wilcoxon tests were used.

The data analysis was done with R and for box-plot analysis SPSS was used.

In our studies, the effect of antiparkinson drugs on sleep was taken into consideration.
Antiparkinson medication's effect on sleep:
Antiparkinson medications may disturb the sleep-wake cycle.
Dopamin agonist treatment has two sort of effect:
1. Direct effect: - sleep-wake regulating system
- circadian rhythm generation

2. Indirect effect: decreasing the parkinsonian symptoms during sleep

Effect of L-Dopa: Increasing REM sleep and REM latency

long-term effect: sedation, enhancing daytime sleepiness

Anticholinerg treatment: increasing REM sleep, decreasing REM latency

MAO and COMT inhibiting agents: increasing REM sleep, increasing daytime vigilance

Changes of sleep pattern in Parkinson's Disease:

Characteristics of sleep pattern:

1. Decrease of TST (total sleep time)

2. Decrease of sleep efficiency

3. Increase of microarousals

4. Increase of WASO (wakefulness after sleep onset)

5. Sleep fragmentation is an early sign, 30-40% of the time spent in bed is awake, waking 2-5 times.

6. Decrease of the number of sleep spindles and SWS duration.

7. Decrease of REM sleep nad REM latency

8. Increase of Arousal Index

Results

Out of neurodegenerative diseases that affect mainly the aging population and negatively influence the quality of life, Parkinson's disease was chosen as the subject of our research. The aim was to establish correlation between the quality of life of patients with Parkinson's disease and some phases of the examinations, regarding the fact that the typical symptoms of Parkinson's disease the non-motor symptoms – which may occur during the early or the late phase of the disease – are getting into the centre of attention. Such non-motor symptoms can be neuropsychiatric dysfunction, dysautonomy, sleep disorder or some sensory symptom such as pain. The occurrence of sleep- and staying awake disorder of patients with Parkinson's disease is 60-98%. Greater part of researches investigating the severity and the nature of these medical conditions have been carried out in relation to patients taking anti-Parkinson's medicinal products, for this reason, side effects of the therapy have also influenced the real appearance of sleep disorders. A wide range of sleep disorders can be detected in Parkinson's disease; there are insomnias, parasomnias and hypersomnias.

Main symptoms of insomnia are difficulties with getting back to sleep, nycturia, REM sleep disturbance (rapid eye movement (REM), sleep behaviour disorder (RBD)), night convulsions, akinesia and tremor. Incidence rate of hypersomnia in relation to Parkinson's patients not taking anti-Parkinson's medicinal products can be compared to the values measured at the healthy control group. Some examinations consider hypersomnia an independent phenomenon appearing in Parkinson's disease, which has no relation to the quality of night sleep or the therapy. Parasomnias appear in the early phase of Parkinson's disease, mostly in the form of REM sleep disorder, this may indicate the later appearance of Parkinson's disease in advance. Sleeping disorder is a frequent symptom and it significantly impairs life quality of Parkinson's disease patients.

There is no unequivocal evidence for the existence of a link between Parkinson's disease and the obstructive sleep apnoea (OSAS) yet2. Nevertheless, the prevalence for OSAS among patients with Parkinson's disease was established between 20 and 66% in the course of the so far examinations. In relation to features of OSAS, there are differences between patients with Parkinson's disease and the general population.

Neurodegeneration that comes along with Parkinson's disease may affect the REM-on and REM-off cell groups that determine the sleep structure, the derangement of which might

appear in the form of sleep fragmentation, decreased sleep efficiency, decreased amount of deep sleep and REM sleep and behaviour disorder during REM sleep (REM Sleep Behaviour Disorder, RBD). REM Behaviour Disorder (RBD) is such a primer sleep disorder that is characterized by the appearance of red striated muscle activity during REM sleep.

During REM sleep without atonia (RWA) an abnormal muscle activation can be detected during REM sleep but without complex behavioural expressions. In the polysomnographic findings of RBD chin muscle enlargement, movement and trepidation of limbs often can be detected during REM sleep. Complex, tough and violent behaviour often emerge. It often causes skin injuries and fractures to the patients and others sleeping in the same bed. Although the clinical symptoms in RBD are quite special and focus attention obviously on the disease, however, other primer sleep disorders such as sleep apnoea can often show similar symptoms. REM sleep appears approximately every 90-120 minutes during sleeping, consequently RBD episodes could arise four times. Rarely it appears only once a week or once a month.

In order to diagnose we need a polisomnographic test to prove the presence of RBD definitively. RBD or RWA appear at 25-50% of patients suffering from Parkinson's disease. The percentage of appearance is even higher in case of MSA and Dementia with Lewy Bodies (DLB). RBD often appears years sooner than the early symptoms of parkinsonism. In the early stage of Parkinson's disease extensive pathological changes occur in the REM sleep controlling – brain stem – areas that take part in the formation of the disease. These observations and also the fact that RBD is extremely rare in Alzheimer's disease - such as in progressive supranuclear palsy - led to a hypothesis that RBD is a forerunner of synucleinopathies.

Most of the patients (87-90%) suffering from RBD are old men. These patients might cause severe injuries to themselves and also to those who sleep in the same bed. RBD can be associated with the neurodegenerative diseases named synucleinopathies. In several written cases the symptoms of RBD appeared 3-13 years earlier than Parkinson's disease emerged. In spite of this, only few researches have dealt with the frequency of RBD in Parkinson's disease patients, however, none of them used PSG recordings and none of them assessed the sleep complaints of Parkinson's disease patients.

In the course of our examination we carried out the complex quality of life examination of (n=50) non-selected Parkinson's disease patients. Sampling was carried out randomly, by

questioning Parkinson's disease patients arriving at the hospital from different parts of the country. There were no preliminary selection criterion or parameters of getting into the examination. 31 men and 19 women took part in the research, their average age is 75,9±11,8 years; average Hoehn-Yahr state 1,9±0,8. Number of patients having the disease for longer than 5-10 years is 48, 2 (41 and 47 years old) men suffer from juvenal PD, their disease started within 2 years. The anonymous subjects gave their written consent to carry out the examination and to use the results for scientific purposes. In the course of the examination we used three, widely accepted questionnaires. The participants were examined and interviewed by a sleep medicine specialist, who used structured questionnaires to examine the sleep disorder and Parkinson's disease: the Epworth Daytime Sleepiness Scale (ESS), the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr Modified Scale. Subsequently, each subject underwent a night polysomnography (PSG) test.

In the course of our comparative analysis when PDQ39 and Beck correlation scale were compared, we found significant correlations between the activity level of every day activity and the measure of depressive state (p: 0,047), between demand for social support and depressive state (p: 0,42), between everyday activity level of PDQ39 and the evaluation of the health condition of the patients (p: 0,013), furthermore between demand for social support and age (p:0,041). We did not discover any difference between the genders.

In the course of the polysomnographic test we found apnoeic and hypopneic episodes at 32 patients. A frequency of 64% of OSAS was detected (32 patients). Prevalence of advanced, intermediate and light OSAS were 22%, 32% and 10%. The average age of patients suffering from intermediate and advanced (AHI>15) OSAS was higher (75 years) than those participants who had no apnoea (p=0.004). In relation to those patients, at whom OSAS was confirmed, we measured significantly higher Epworth values (p=0.05). The most frequent symptom of patients with apnoea was snoring (78%), along with 80% sensitivity. The most specific symptom was apnoea detected by the sleeping partner (92%).

RWA is significantly more among patients with Parkinson's disease than in the healthy control group. Furthermore, nearly in two-thirds of patients with Parkinson's disease the submental tonic EMG activity was detected in at least 20% of the total REM sleep period. REM Sleep without atonia can be detected in the case of several patients with Parkinson's disease.

With our research we intended to highlight that Parkinson's disease patients suffer not only from physical inconveniences and lowered level of activity, but also from distress and depression. Psychological or social therapies appropriate to treat anxiety and depression have to be highlighted in the course of improving the quality of life of Parkinson's disease patients. These therapies are indispensable in order to maintain interpersonal relations, personal and social competences.

Parkinson's disease impairs the REM sleep moduling centres by involving the lower brain stem much sooner than the formulae of the bridge and the substantia nigra. Locus ceruleus is affected in the disease by all means. Studies have proved the damage of locus coeruleus neurons and cholinergic neurons. 40% decrease of cholinergic neurons, the appearance of Lewy Bodies in the lower brain stem and in the pedunculopontine tegmental core indicate obviously the confusion of the influence of REM sleep.

OSAS is a major pathological condition among Parkinson's disease patients. Within this population, its appearance is more likely among old patients. Parkinson's disease patients with apnoea are more prone to sleep during the day than non-apnoeic patients. Their most sensitive symptom was snoring, and the most specific one was apnoea detected by the sleeping partner. The Obstructive Sleep Apnoea Working Group of the EU Driving Licence Committee drew up the Brussels Questionnaire in 2013. The reason behind was to make OSAS screening accessible for those who apply for a driving licence. This examination was conducted on patients with Parkinson's disease as well. On the basis of surveys, it can be stated that using a private vehicle plays an important role in the life and quality of life of the population. Our aim is to conduct OSAS prevalence research (applied in Parkinson's disease) among those Parkinson's disease patients who have a driving licence. This objective of ours is relevant for two reasons. On the one hand, the presence of OSAS is a further risk factor in relation to patients involved, on the other hand - and deriving from the first one -, appearance of clinical symptoms of OSAS at patients with Parkinson's disease may result in losing driving licence, either in the short term or in the medium to long term, which at the same time, may involve with the change of quality of life. Based on the results of a retrospective survey, in relation to patients at stage 2-3 of Hoehn-Yahr, number of collisions is significantly higher.

The Brussels recommended questionnaire may be a proper, simple tool of OSAS screening of Parkinson's disease patients and driving licence applicants by making multidisciplinary assessment possible; driving related risk factors of patients could be assessed objectively, it reinforces safe transport and this way the number of road traffic accidents can be lowered.

The 1., 2. and 3. hypothesis is supported by the research findings described above.

The 4. hypothesis of my research results described above prove only partially.

Results of my dissertation

Extensive research is conducted worldwide in order to improve the quality of Parkinsonian patients' life. Regarding the subjects and relations of my study, such a complex assessment of life quality has not been done in Hungary yet. I used both subjective and objective measurement tools in my research. I did not have an opportunity to compare the results of the ESS and PDSSII subjective questionnaires to national literature because of the absence of study results. Comparing my study results to international data, my new conclusions and results as follows:

1. The value and SD of the Epworth was 5,52±2,25. This did not verify a more excessive daytime sleepiness compared to the healthy population. According to the international literature data Parkinsonian patients' ESS was 4.9 ± 3.63, when at healthy people it was 2.17±2.54. ($P<0.05$) Other research found a 6,21± 3.63 ESS value at PD patients and a 3.21±1.71 at healthy subjects ($P<0.05$).
2. We found a 25,07±13,45 mean value with the PDSS questionnaire. At every item out of 15, our patents gave 4-5 points. This verified an average degree of sleep quality deterioration. The results of the two observed international studies showed a significant standard deviatio. Our results lay in between. The significant international deviation in the use of the PDSS makes the examiner uncertain. **It underlines the huge subjectivity of the questionnaire.** During RWA (REM sleep without atonia), we find abnormal muscle activation without complex behavioural manifestations at REM sleep.

   In the RBD polysomnography reports, we often see movements and clonisations of the limbs at REM sleep. Complex, vehement, often violent behaviours might occur.
3. RBD patiens had a much higher limb movement index at REM phase (18,6±4,39 event/hour) than the control group (4±2,3 event/hour, p=0,0001).
4. RBD patients spent more time in slow wave sleep during their sleep (2,64±1,31% than the control subjects (0,76±0,27%, p=0,004).
5. They also had a higher rate of REM sleep (12,8±3,19% vs. 8,6±1,67%, p=0,01), however, their REM density was lower (20,8±2,77% vs. 31,2±4,16%, p=0,01).
6. PD patients spent a lower rate of their REM sleep in muscle atonia than the control subjects (61,5% vs 95,6%, p=0,004)

According to our study results, half of the RBD patients would have been unrecognised if only the clinical questionnaires had been used to obtain a diagnosis. PSG is the effective tool to investigate the non-motor sypmtoms.

With our studies – including polysomnography tests -, we would like to emphasise that the RBD is an important risk factor and can be an early sign of Parkinson's Disease. Close monitoring of the RBD patients could help the early recognition of neurodegenerative diseases and may create a possibility for the effective mapping of neuroprotective mechanisms and for the improvement of the quality of these patients' life.

The EU Driving License Committee's Obstructive Sleep Apnoea Working Group created the Brussels Questionnaire in 2013. The aim of the questionnaire is to screen those, who apply for driving license, for OSAS. Our polysomnography tests found episodes with apnoe or hypopnoe at 32 patients.

7. We measured a 64% prevalence of OSAS (32 subjects). Prevalence of severe, moderate and mild OSAS was 22%, 32% and 10% respectively. Patients suffering from moderate and severe (AHI>15) OSAS had a higher average age (75 years) compared to those who did not have apnoe. Those with OSAS had significantly higher points at the ESS. (p=0.05)

8. The most common symptom of the OSAS patients was snoring (78%) with a sensitivity of 80%. The most specific symptom was apnoe observed by sleeping partner (92%).

There is no clear evidence of any correlation between Parkinson's Disease (PD) and obstructive apnoe syndrome (OSAS) yet. Nevertheless, prevalence of OSAS among PD patients was found to be 20-66% in studies conducted so far. Certain characteristics of OSAS are also different in PD patients than in the general population.

We measured the prevalence of OSAS occuring at PD patients at subjects who had driving license. We considered two factors. First: presence of OSAS is an additional risk factor for the patients. Second: as a result of the above, appearance of clinical signs of OSAS at PD patients can lead them to lose their driving license – either in the short or the long run – which effects the life quality as well.

The Brussels Questionnaire can be an appropriate, simple screening tool for OSAS among those who suffer from PD or who apply for driving license.

These are the new conclusions and results of my research.

Conclusions

With my research I intended to highlight that all phenomena are related to the basic symptoms of the disease (muscle stiffness, slow movements, steady-state tremor), furthermore they are related to social separateness and emotional instability deriving from the disease. Along with physical inconvenience and decrease in activity level, patients suffering from Parkinson's disease suffer from oppression, depression and insomnia as well. Psychological or social therapies appropriate to treat anxiety and depression shall be highlighted in the course of improving the quality of life of Parkinson's disease patients, which therapies are indispensable in order to maintain interpersonal relations, personal and social competences.

The aim of further studies might be the examination of the effect and efficiency of complementary (non-drug) therapies on life quality in the course of healing process and rehabilitation.

The 1, and 2, hypothesis is supported by the research findings described above.

Parkinson's disease impairs the REM sleep moduling centres by involving the lower brain stem much sooner than the formulae of the bridge and the substantia nigra. Locus ceruleus is affected in the disease by all means. Studies have proved the damage of locus coeruleus neurons and cholinergic neurons. 40% decrease of cholinergic neurons, the appearance of Lewy Bodies in the lower brain stem and in the pedunculopontine tegmental core indicate obviously the confusion of the influence of REM sleep.

RWA is significantly more among patients with Parkinson's disease than in the healthy control group. Furthermore, nearly in two-thirds of patients with Parkinson's disease the submental tonic EMG activity was detected in at least 20% of the total REM sleep period. REM Sleep without atonia can be detected in the case of several patients with Parkinson's disease.

By means of my research I would like to raise awareness of the acknowledgement of RWA as a risk factor, which might be important in case of diseases having such long period of incubation as Parkinson's disease. Close monitoring of patients suffering from RBD would enable us to diagnose neurodegenerative diseases early, which could form a basis for the effective and efficient exploitation of neuroprotective mechanisms.

OSAS is a major pathological condition among Parkinson's disease patients. Within this population, its appearance is more likely among old patients. Parkinson's disease patients with apnoea are more prone to sleep during the day than non-apnoeic patients. Parkinson's disease is a complex neurodegenerative disease leading to motor, cognitive and visual impairments, any of which influences capability to drive. However, no substantiated epidemiologic data are available about road accidents caused by patients suffering from Parkinson's disease.

The 3, hypothesis is supported by the research findings described above.

Our aim is to conduct OSAS prevalence research (applied in Parkinson's disease) among those Parkinson's disease patients who have a driving licence. This objective of ours is relevant for two reasons. On the one hand, the presence of OSAS is a further risk factor in relation to patients involved, on the other hand - and deriving from the first one -, appearance of clinical symptoms of OSAS at patients with Parkinson's disease may result in losing driving licence, either in the short term or in the medium to long term, which at the same time, may involve with the change of quality of life.

The Brussels recommended questionnaire may be a proper, simple tool of OSAS screening of Parkinson's disease patients and driving licence applicants by making multidisciplinary assessment possible; driving related risk factors of patients could be assessed objectively, it reinforces safe transport and this way the number of road traffic accidents can be lowered.

The 4, hypothesis of my research results described above prove only partially.

List of own publications

Original publications related to the topic of the dissertation

1. Nóra Pető, Terézia Seres, Zoltán Szakács, Veronika Fáy, Jelena Karaszova, Andrea Kontra, Olivia Lalátka, Gyula Domján

Evaluation of the Brussells Questionnaire as a screening tool for obstructive sleep apnea syndrome

NEW MEDICINE 21:(1) pp. 3-7. (2017)

2. Terézia Seres, Mária Csóka, Zoltán Szakács, Éva Kellős, NóraPető, Andrea Kontra Gyula Gyula

Life quality assessment of patients with Parkinson's disease using subjective measuring instruments

IME: INTERDISZCIPLINÁRIS MAGYAR EGÉSZSÉGÜGY / INFORMATIKA ÉS MENEDZSMENT AZ EGÉSZSÉGÜGYBEN 16:(7) pp. 27-30. (2017)

3.TeréziaSeres, Zoltán Szakács, Nóra Pető, Éva Kellős, Veronika Fáy, Jelena Karaszova, Andrea Kontra, Olivia Lalátka, Gyula Domján

Sleep-related breathing disorders in Hungarian patients with Parkinson’s disease

NEW MEDICINE 21: (1) pp. 8-13. (2017)

4. Mária Csóka, Sándorné Molnár, Éva Kellős,Gyula Domján,

Problem-solving nursing care model for Parkinson's disease

ORVOSI HETILAP 157: (22) pp. 855-868. (2016)

5. Seres Terézia, Szakács Zoltán, Kellős Éva, Simon Márta, Terray Horváth Attila, Fáy Veronika, Karaszova Jelena, Kontra Andrea, Lalátka Olivia, Csóka Mária, Domján Gyula

Research on ropinirole treatment of restless leg syndrome

NEW MEDICINE 20:(2) pp. 42-52. (2016)

6. Zoltán Szakács, Terézia Seres, Éva Kellős, Márta Simon, Attila Terray Horváth, Veronika Fáy, Jelena Karaszova, Andrea Kontra, Olívia Lalátka, Mária Csóka, Gyula Domján

Prevalence of REM behavioral disorder and REM sleep without atonia in patients suffering from Parkinson’s disease

NEW MEDICINE 20: (3) pp. 86-91. (2016)