SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Examination of neuropsychiatric symptoms in major neurocognitive disorder

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The Examination (online format) takes place 12:00, on January 20th, 2021.

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Publicity is guaranteed during the online Defense. If you are willing to participate, please indicate via e-mail to majer.reka@med.unideb.hu until 12:00 on January 19th, 2021.
Due to technical reasons later sign-ups are not possible and you will not be able to join the online Defense.

1. Introduction

Dementia is one of the greatest challenges in the 21st century and the most significant health crisis because the main risk factor of dementia is old age itself. The global aging of the population has been directly related to the diseases' incidence. In 2015 we have known almost 47 million dementia patients on a world scale. The number of patients is doubling every 20 years for this reason in 2030 nearly 75 million, in 2050 more than 130 million dementia patients can be expected worldwide. This could mean even 10 million new patients in a year therefore a new dementia patient approximately could be diagnosed every 3 seconds.

The rapid growth of dementia cases requires urgent actions, especially in countries with low or middle income.

In Hungary, the numbers of dementia patients are around 250 thousand at present but the European countries have about 10 million patients. However, it is important to keep in mind that the disease has not just got a very significant impact on the patient's life but also has on impact on his/her family, friends, and caregivers' life, too, which means the multiples of patient's number.

The illness-related costs are estimated at $604 million yearly in 2010 which are grown to $818 million by 2015 which exceeds 1% of the global GDP. It meant a 35% growth. The capacity of the institutional care system, for which ensure care for the dementia patients, has been struggling with some deficiencies, however, we should notice that one of the best and the most economical solution as regards the quality of life of the patients is the ability of the patient to remain in his/her own home as long as he/she can.

Many data and estimates make it clear that action is needed in the dementia care system. In addition to the action plans besides the prevention, there is a lot of emphasis on the steps of the care expenses' reduction.

The aim of our research is to highlight the symptomatic image of dementia patients from another aspect which is new and we have not focused on it yet. In our research we were built on the behavioral and psychiatric symptoms instead of the cognitive functions because the recent research results were pointed out that this syndrome has shown more importance of the everyday lifestyle of the patients and it related to the patient' ability to remain in his/her own home, which could mean the most cost-effective solution for the care of the dementia patients.

2. Scope

The new DSM-5 was published in 2013 which made the classification and the diagnostics of dementia a new connotation. In the case of this, a new definition was created, which is called major Neurocognitive disorder (mNCD), instead of the definition of dementia. The main reason to become a new defining because of the negative attitude and associations of dementia. The NCD has not got a stigmatizing effect, and it includes the wider variations of the symptoms and conditions. NKZ no longer has a stigmatizing effect and encompasses a wider range of symptoms and conditions. A summary paper published in Nature Reviews Neurology in 2014 reviews the overlaps and differences between dementia and major neurocognitive impairment and clearly argues that major neurocognitive disorder is synonymous with dementia. In the following, accordingly, I use the term mNKZ (major neurocognitive disorder) to denote the disease and describe the symptomatic background based on the latest DSM-5.

2. 1 Neurocognitive disorder

This new defining, which is known from the DSM-5, includes those groups of diseases in which the damage affects cognitive functions. In the case of NCD, the cognitive performance impairment is not related to birth and it does not exist from early childhood. This is an acquired disease in which the performance of the cognitive function is getting worse compared to an early condition. The definition of the DSM-5 is the following:

major Neurocognitive Disorder

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:

1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and

2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

The etiology of the major neurocognitive disorder

The two most frequent aetiological forms of dementia are Alzheimer's disease and vascular dementia; the occurrence of a mixed form is also common. Besides, many other types are known. In our study, we just research the types of Alzheimer's disease, vascular disease, and the multiplex etiology. Accordingly I present the criteria system of these three.

- Major Neurocognitive Disorder Due to Alzheimer's Disease

A. The criteria are met for major or mild neurocognitive disorder.
B. There is insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired).
C. Criteria are met for either probable or possible Alzheimer's disease as follows:

1. Evidence of a causative Alzheimer's disease genetic mutation from family history or genetic testing.

2. All three of the following are present:

a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing).

b. Steadily progressive, gradual decline in cognition, without extended plateaus.

c. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).

- Major Vascular Neurocognitive Disorder

A. The criteria are met for major or mild neurocognitive disorder.
B. The clinical features are consistent with a vascular etiology, as suggested by either of the following:

1. Onset of the cognitive deficits is temporally related to one or more cerebrovascular events.

2. Evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function.

C. There is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits.
D. The symptoms are not better explained by another brain disease or systemic disorder.

- Major Neurocognitive Disorder with multiplex etiology

In case of many patients who have been struggling with Alzheimer's disease, this can be associated with cerebrovascular disease and it is true back and forth. Many patients who have been struggling with vascular disease consequence that the Alzheimer's disease develops as the years go by. These types of disorders we call major neurocognitive disorder with multiplex etiology. However the studies about it a little bit controversial because it seems that the multiplex etiology cases present worse performance and the outcome of the disease is more serious.

2.2 Neuropsychiatric symptoms/ Behavioral and psychological symptoms of dementia

Dementia is primarily known as the disease of cognition and executive functions but the behavior change and the psychological symptoms in many cases form an integral part of the clinical aspect. We call this syndrome the behavioral and psychological symptoms of dementia.

The International Psychiatric Association (IPA) introduced the term BPSD (IPA Complete Guides to Behavioural and Psychological Symptoms of Dementia) in 1996. BPSD is considered a non-disease–specific clinical syndrome, a sub-syndrome that consists of heterogenic psychiatric symptoms. The interaction of biological, psychological, and social factors is assumed to be behind the development of BPSD. The significances of BPSD are that their cost-efficient indicators are much higher than the cognitive symptoms' indicators. Because of the new classification system in the DSM-5, this syndrome has changed the

definition that is why recent we call it neuropsychiatric symptoms=NPS instead of BPSD. As part of the NPS can appear any kind of psychiatric symptom. We can differentiate the types of neuropsychiatric symptoms which are psychomotor, psychiatric, and behavioral symptoms. Psychomotor disorders are wandering and agitation; psychiatric symptoms are affective symptoms, anxiety, hallucination, and delusion; behavioral symptoms are aggression, sleeping, and eating disorder. It is very common that the symptoms can be mixed and the numbers of the symptoms increase the years go by.

For the clinician, it is simpler to differentiate and define cognitive symptoms related to dementia and scale their severity than to define and treat the secondary symptoms. This is partly the reason why greater attention is paid to these symptoms by clinicians and scientists. In the studies, we could read that these symptoms, however, they were known as a secondary syndrome, got much higher attention because of the quality of life of the patient, these are a very important determinant of the patient-experienced distress, the caregiver distress, and the prognosis of the disease.

Regarding the costs, the neuropsychiatric symptoms mean the biggest problem in the major neurocognitive disorder. The frequency and the severity of the NPS are greatly variable and can appear at any stage of the disease. The significances of them are the following: progressed the disease without appropriate treatment, make the daily activity worse, decrease the quality of life, and increase to use many times the health care. For this reason, the costs of the care are increasing which is ending to take the patients in a care institute in their early stage.

In the literatures, we could find especially extreme data about the epidemiology of the neuropsychiatric symptoms which depend on where the research was taken such as at their home, in a hospital or in a care institute. In addition to this, the severity of the major neurocognitive disorder was affected by the results. Overall we could see that in minor neurocognitive disorder 50% is the frequency. In the major neurocognitive disorder, the frequency of the neuropsychiatric symptoms have changed between 20- 90 %, which has depended on the severity of the symptoms. 40% of the patients who have been involved presented more than 1 symptom and in many cases, it could be more than 5.

We could experience a quite high variability about the time course of the NPS. According to previous data, 20-30 months before a diagnosis could appear affective symptoms, depression, suicidal thoughts, and increasing social isolation with the frequency of

10-60%. Then 8-10 months before a diagnosis could appear delusions especially micromaniac or nihilistic, self-blame, and anxiety symptoms besides the upset of the circadian rhythm. In the year following the clinical diagnosis can occur emotion lability, sensitivity, agitation, and wandering with a frequency of 40-80%. In the following years, hallucinations and aggression can appear with the frequency of 20-40%.

In some types of the NCD, we can see a different patterns with the incidence of the NPS. In AD firstly agitation, irritability, apathy, and depression appear. Hallucinations and delusion are more common. In the dementia of the Lewy-test misidentifications and hallucinations appear most often firstly in a visual form. In the case of fronto-temporal dementia mainly we can see disinfection, disinhibition, and stereotypical behavior, besides a rough change in appetite could appear in both ways. Affective symptoms and apathy mostly relate to the etiology of the vascular, which in many times associated with anxiety symptoms and psychotic symptoms.

The biggest significance of the NPS is that these symptoms are the most important reason for the placement in an institution and it is associated with the increased mortality risk. In the decision of the placement in an institution, the caregiver's stress is eminently important which mainly can be traced back to the NPS and the age of the caregiver, the type, and the seriousness of dementia.

However, the patients themselves have been suffering from the NPS, but their consequences have a great impact on the caregivers and society, too. It is associated with emotional anxiety, quality of life deterioration, accidental injuries, the faster progression of cognitive impairment, greater functional impairment (that is related to the high risk of institutionalization), more frequent hospital care, increasing risk of abuse and neglect (including the unconsciousness), and decreasing survival. The economic burdens are shocking: The NPS gives 30% of the care costs who has been suffering from major neurocognitive disorder.

Results of the research have not just confirmed that this syndrome has a big impact on the physical and mental health of the relatives but also its impact is more significant than cognitive symptoms.

3. Aims

Based on the literature presented above that the neuropsychiatric symptoms are common in major neurocognitive disorders and they are significantly associated with the caregiver's burden and the increasing cost of the disease. The appropriate defining and the evaluation of these symptoms are the finals steps in the diagnosis of neurocognitive disorders.

As we know that our research is the first Hungarian research which studied systematically the neuropsychiatric symptoms in patients with a major neurocognitive disorder, without the examination of any pharmacology effect.

Our primary aim was the evaluation of frequency and severity of the neuropsychiatric symptoms compared to the national patients with major neurocognitive disorder. We expected that we could see the same frequency and severity rates as in the previous research results which confirmed the significance of the symptoms.

The secondary aim of our study was that we have examined the connection between the cognitive functions and the neuropsychiatric symptoms over and above neuropsychiatric symptom pattern with the aim of our results contribute to the clinical differentiation of the major neurocognitive disorder types, especially to the Alzheimer's disease and vascular dementia. Based on the previous literature information's we assumed that the neuropsychiatric symptoms have presented a specific pattern in the several etiology of the major neurocognitive disorder.

Our third aim was to examine the quality of life of patients with a major neurocognitive disorder, the psychological burden of the disease, impairment of daily activity, and the frequency of depression in old age then we studied them from the perspective of the cognitive functions and the neuropsychiatric symptoms.

Last but not least our aim was that we have surveyed from the relatives' perspective the neuropsychiatric symptoms and cognitive functions' the impact of its burden on the everyday life because as the above literature presented that syndrome has meant the greatest burden for caregivers.

Based on the literature data presented above in our research we set up the following hypotheses:

- The incidence of neuropsychiatric symptoms is around 90% in a Hungarian sample.
- There is a difference in the frequency of neuropsychiatric symptoms in neurocognitive disorders with different etiology.
- The deterioration of the cognitive functions are associated with the severity and the frequency of neuropsychiatric symptoms.
- The NPS expressively affect the patient's quality of life and illness intrusiveness.
- The effects of the NPS will have an important impact on caregivers' burden, and this is stronger than the effects of the cognitive functions

4. Material and methods

The locations of our study area in the dementia specialist practice at the Psychiatry Clinic and Neurology Clinic of the Clinical Centre of the University of Debrecen. The survey selected samples from patients who were presented between February 2013 and April 2015. Before this the research planning and the licenses' supplying have happened.

These patients were included in the survey of those who attended for the first time and were referred by their GP.

Additional criteria were that normovigilance and they lived in their homes with their family members, not in a nursing home or other nursing facility, and a family member with whom they were living accompanied them to the examination.

Exclusion criteria were hearing and/or seeing impairment and chronic depression (i.e., the no history of antidepressive therapy depression) or other psychiatric diseases in the anamnesis that would have influenced the completion of the tests.

The examinations were carried out together with the patient and their caregiver. The necessary information was verbally explained to them before the examination commenced and a consent form was also signed by the patients.

This research was performed in accordance with the latest version of the Declaration of Helsinki. The study was also approved by the local ethics committee and all the included subjects submitted a written informed consent.

The research was materialized by the permission of the Hajdu Bihar County Government Office Public Health Administration. Research protocol identifier: DE OEC RKEB/IKEB 3773-2012, case number of license: IX-R-052/00306-1/2013.

In the research, all in all 131 patients were involved.

4.1 Study presentation

After collecting demographic data and anamnesis based on a clinical interview, we performed a detailed neuropsychological examination focusing on the cognitive deterioration, NPS, quality of life, illness intrusiveness, impairment of daily activity, geriatric depression, and the burden on relatives. The evaluation process took approximately 40-50 minutes per patient.

The neuropsychological examination was carried out with the joint participation of the patients and their relatives in the following way:

At the beginning of each consultation day, we checked with the coordinating assistant who have been the newcomers. Firstly we registered the patient then we read out the patient's anamnesis if the selection criteria were right we could tell the aim of the research for the patient. In case the patient verbally agreed with the examination then I led the patient and his/her relative into a specific test room provided for this purpose. After they had signed the statement of consent the examination began.

In the first part of the study, I discussed with the patients and their relatives that we were doing some tasks to survey the cognitive functions but before this, we were talking about their everyday life and other symptoms. Firstly they answered the demographic questions which were followed with the detailed anamnesis-recording. In the second part, the patient's mental status was assessed. As part of this, I assessed the quality of life, the burden of disease, which I expected the patient to answer. This was followed by the third part of the study, the mapping of neuropsychiatric symptoms, where for each symptom I asked one by one about the frequency and severity of the symptom. We expected an answer from these relatives. Symptom testing was answered based on helpful questions in the NPI test guide. Then, in connection with the symptoms, I also asked the relative how much burden it means for a symptom as a caregiver. The fourth part of the study was cognitive tests.

The sequence of the study was an important part. Based on the previous studies in many cases the researchers were warned that the procedures for measuring cognitive functions especially the failed attempts made the patient upset, anxious, impatient and these mood swings could have been an impact on the next questions that is why the cognitive tests are the last research.

During the research, we got some information about the patient most of all about the NPS because many times the patients have presented behavior symptoms which the patients and their relatives negated before it, for example, verbal aggression, irritability, and not appropriate behavior for social norms, etc.

It was also important about the research to clarify that the result has not had an impact on the later treatment or the patient development because in many cases the relatives thought that the test results of the patient could have been an impact on the later hospitalization or

hospital care because of this relatives wanted to make the symptomatic picture better or worse.

Upon completion, the selected patients underwent a thorough neuropsychological examination, which took approximately 45-50 minutes.

Categorization of the patients:

Patients who received the clinical diagnosis of dementia in the outpatient clinic were further divided into 3 groups: Alzheimer's-disease (AD), vascular dementia (VD), and mixed dementia (MD). The diagnosis of dementia and assigning diagnosed patients to three different subtype groups were based on a routine clinical decision protocol that included detailed anamnesis, neuropsychiatric and somatic examination, laboratory tests, CT and/or MRI scans. This protocol followed the usual clinical practice of the evaluation and diagnosis of dementia in participating specialist centers.

Demographic data:

A total of 131 patients were selected for our sample. The patients were 100% Caucasian. Gender ratio: 48 men (36%) / 83 women (63%). The mean age of the patients was 77 years (SD = 8.3). In terms of age distribution, nearly 50% of patients were in the 80-89 age group and more than 30% were in the 70-79 age group. The 70-89 age group accounted for nearly 80% of the sample. The youngest patient was 52 years old and the oldest was 93 years old. In terms of relationship status, married and widows accounted for nearly equal proportions in the sample, 46% -45%, which together accounted for more than 90% of the sample. In terms of educational attainment, the proportion of those with a high school diploma and those graduating from grades 7 to 12 was similar, accounting for more than 60% of the sample. The proportion of those with 6 elementary and technical degrees was around 10%. College and university degrees occurred in 8%.

Altogether 131 patients were included in the study. The mean age was 77 years (SD=8.3). 55 patients were assigned to the AD group, 33 patients were assigned to the VD group, and 43 patients were assigned to the MD group. The gender ratio was: 48 men/83 women. There were no significant differences across groups regarding gender distribution and age.

4.2 Methods

The following tests were implemented:

WHO Well-Being Index short version (WBI-5):

Well-Being Index is amongst the most widely used measuring instrument. It is a self-reported questionnaire about psychological well-being that is used in clinical and monitoring studies. The WHO's 5-item Well-Being Scale is used to collect information about the person's general well-being from the previous 2 weeks. A validated Hungarian variation is used. The WBI-5 is a short questionnaire consisting of 5 simple questions, which tap into the subjective well-being of the responders.

Illness Intrusiveness Rating Scale (IIRS):

This is a short questionnaire developed by Devins and his colleagues to measure disease intrusiveness. It contains 13 items and the scale ranges from 1 to 7. Higher scores show greater intrusiveness. The underlying concept is that illnesses limit activities that are important for the individual and it interferes with lifestyle and quality of life – which is called illness intrusiveness.

Activity of Daily Living Scale:

Activity of Daily Living Scale contains daily vital functions which are so simple to do every day and they are required for an independent way of life. Scale is widely used to follow dementia patients' daily activity.

Geriatrics Depression Scale Short Form:

The scale contains 15 questions that are primarily related to the value, emptiness, boredom, usefulness, and the interest of life. Referred to the results of the search the GDS' short version is appropriate to survey the depression in old age.

Mini-Mental State Examination (MMSE):

The most widely used quick cognitive screening test in international practice has been extensively used to assess individuals' cognitive function. The MMSE score ranges from 0 to 30, with higher scores indicating better cognitive function.

This method was used during the clinical assessment in the diagnosis of neurocognitive disorder. However, the MMSE results were not included in the analyses because the ADAS-Cog test seemed to be more adequate in evaluating the cognitive functions

of the patients from a wider perspective. Besides because of the MMSE test's widespread and accessibility widely (for example internet) in many cases, the patient has been facing the questions many times which can reduce the score. During the research, there were many cases which showed that patients practiced certain tasks with the relative, for example, the daily date.

Modified Mini-Mental Questionnaire (MMMS, 3MS):

Modified Mini-Mental Questionnaire have been studying widely the cognitive functions and their scores present the cognitive impairment 'extent that is why it is easier to tell how serious dementia is.

Alzheimer's Disease Assessment Scale-Cognitive Test (ADAS-Cog):

ADAS-Cog is one of the most popular cognitive testing instruments in Alzheimer's-related clinical diagnostic work and research. It consists of 12 subscales, which are pivotal in assessing and monitoring dementia patients. Although this test is mainly used in Alzheimer's patients, it is also commonly exploited in other types of dementia as the tests are suitable for generalization. The validation of the Hungarian version is by Pákáski *et al*.

Neuropsychiatric Inventory (NPI):

NPI was developed by Cummings et al. to assess dementia-related behavioral symptoms. The NPI examines 12 symptoms of behavioral and psychological functioning: aberrant motor activity, agitation/aggression, anxiety, apathy, appetite and eating abnormalities, delusions, disinhibition, dysphoria, euphoria, hallucinations, irritability/lability, and, night-time behavioral disturbances. The NPI can screen for NPS in neurocognitive disorder. The NPI is assessed based on the caregiver's report

Behavioral Pathology in Alzheimer's disease (BEHAVE-AD):

BEHAVE-AD is a screening device which can evaluate behavioral disorder in patients with Alzheimer's disease. BEHAVE-AD surveys 7 areas: delusions, hallucinations, aberrant motor activity, aggression, diurnal rhythm disorder, anxiety, and emotional disorders. NPI has been surveying more areas than BEHAVE-AD but in the case of the symptoms in it, the nature of the symptom could be revealed more precisely with the help of the questionnaire, for example the types of hallucinations and delusions, etc. Because of this during the research, we used both procedures for measuring neuropsychiatric symptoms to understand deeper the symptomatic picture.

Statistical analysis

Statistical analysis and data management were performed by Stata (StataCorp. 2009, Stata Statistical Software: Release 11. College Station, TX StataC) statistical program. The indicated statistical significance was $p<0.05$. For data analysis, we applied descriptive statistics to present the main characteristics of the sample, calculating the mean and standard deviations. For inferential analysis, Pearson's chi-squared and Fisher's exact test were used to examine the differences between the groups and categorical variables. For the analysis of associations between categorical and continuous variables, either ANOVA or Kruskal-Wallis test were applied depending on the normal versus non-normal distribution of the data. And for correlation analysis, Pearson's correlation coefficient was used and linear regression. To define the strength of the correlation, we used Akoglu's user guide, which provides a recommendation for interpreting the correlation coefficient in psychological articles.

5. Results

5.1 Results of cognitive functions' research

Cognitive functions were evaluated with the MMSE, MMMS, and the ADAS-Cog. The m**ean score was 17.3 (SD=5.69) for the MMSE, and 39.64 (SD=14.15 range 8–66) for the ADAS-Cog.** There was no significant difference by ANOVA test between the diagnostic groups regarding the severity of cognitive deterioration as measured by the three tests.

These groups are homogeneous in terms of cognitive functions. Referred to the results we can see that the sample is a moderately serious dementia population.

Patients with mild cognitive impairment were excluded, i.e., had an ADAS-Cog score below 8 or an MMSE score above 23. A mean MMMS value of 45 points indicates a moderate decline where self-sufficiency requires control. The minimum MMSE score was 3, the maximum was 23. Overall, 52% of patients were in the moderate category with an MMSE score of 19–10, 38.5% were in the mild category with an MMSE score of 23–20, and 9.6% were severe category with an MMSE score below 9.

5.2 Results of NPS

For surveying the NPS we used two questionnaires which had been the NPI and the BEHAVE-AD. In the cases of both questionnaires, we studied the total scores and analysed the symptoms one by one. In terms of the NPI scale, we examined separately the frequency and severity of symptoms.

The occurrence of NPS in our sample was 100%, all patients showed NPS. The minimum number of symptoms was 2, and the maximum was 11. The most common number of symptoms was 4.

The mean NPI total score was 44.0 (SD=22.7; range 11-103). The mean of the NPI scale frequency score: 14.58 +/-7.55 (3 -36), the mean of the severity score subscale: 12.87 +/-6.42 (3 - 29). With respect to individual symptoms, based on frequency scores, motor disturbance (2.7 [SD=1.2]), depression (1.8 [SD=1.2]), agitation/aggression (1.7[SD=1.2]), and appetite/eating changes (1.4 [SD=1.3]) were the most frequent in the total sample.

The following symptoms present moderate frequency such as anxiety, delusion, night-time behavioral disturbances, irritability/lability, and hallucination. The least common symptoms are apathy/indifference, disinhibition and elation/euphoria.

With the help of the ANOVA test, we studied that in terms of the total score there could be any difference between the groups, but at the significance level, we could see that there were no significant differences across study groups in the mean total score, mean frequency score, and mean severity score of NPI.

Because there was not any significant difference between the groups in terms of the neuropsychiatry symptoms' total score, that is why in the next step we studied that in terms of particular symptoms there were any differences between the three groups. A comparison of the three groups were made in terms of the frequency of NPS and the results of the Fisher Exact test so we have found significant difference regarding the delusion, hallucination, disinhibition, and frequency of motor disturbance.

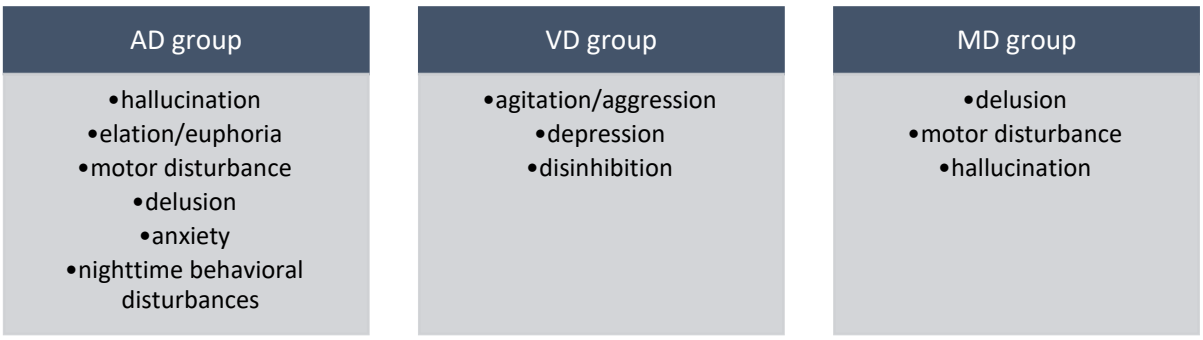
In the AD group, the hallucinations and the motor disturbance are more common, in the VD group the agitation/aggression, depression, and disinhibition behavior are more common and in the MD group, the delusions and the motor disturbance are more common.

Considering the severity of symptoms, **the most severe symptoms turned out to be motor disturbance (mean 2.32 [SD=1.04]), agitation/aggression (mean 1.61 [SD=1.1]),**

depression (mean 1.59 [SD=0.99]). Moderately severe symptoms are appetite/eating changes, delusion, night-time behavioral disturbances, anxiety, irritability/lability, and hallucination. The least severe symptoms are apathy/indifference, disinhibition, and elation/euphoria.

In terms of the severity of symptoms we have found a significance difference in the case of the following symptoms: agitation/aggression, disinhibition, hallucination, and anxiety. In the AD group the delusion, hallucination, anxiety, elation/euphoria, motor disturbance, and night-time behavioral disturbances are more severe, in the VD group the depression, agitation/aggression, and disinhibition are more severe, and in the MD group, the hallucination and delusion are more severe.

Summarizing the symptoms in which we have found significant differences between the groups.



We could see that our initial hypothesis in which the dementia-specific NPS sample has been confirmed. Based on our results in terms of Alzheimer's type dementia there are some symptoms which are more common and severe: elation/euphoria, motor disturbance, nighttime behavioral disturbances but in the case of vascular ‘origin the mood life symptoms are more common. NPS profile of mixed diseases is mostly similar to the neurodegenerative ‘origin.

5.3 Results of between the NPS and cognitive functions relationship

We examined the relationship between the level of cognitive deterioration as measured by the ADAS-Cog, and the frequency and severity of NPS as measured by the NPI test. We surveyed the connection between the level of cognitive deterioration which is measured by ADAS-Cog and the frequency and severity of NPS which is measured by the NPI test. **NPI**

total score, frequency total score, and severity total score were significantly associated with the ADAS-Cog total score ($p < 0.0001$ based on Kruskal-Wallis test, and $p= 0.0002$ based on ANOVA). We did Pearson's correlation analysis to examine the intensity of the connection. Regarding the results r=04 beside the correlation coefficient, we can see the meanly intense connection between the ADAS-Cog's total scores, NPI's total scores and the frequency and severity's total scores.

After the total scores, we also studied the individual neuropsychiatric symptoms that between these could have been any connection with the impairment of cognitive functions. Individual NPS also showed significant association with the ADAS-Cog score, specifically apathy/indifference, irritability, nighttime behavioral disturbances, appetite/eating changes, motor disturbance, and disinhibition. Results indicated that a lower levels of cognitive functions were associated with higher frequency and more severe presentation of these NPS.

5.4 Results of the psychological indicators

The average WBI-5 was 40.5 +/- 21.1. In addition, the result can be interpreted by percentage, on average the patients could live a 40% well-being. Between the three groups, there was not any significant differences (p=0.5068). **Quality of life shows a pronouncedly significant relation with NPI total score (r=-0.6, (r2=0.35), ANOVA F (1,129) =71.62, p<0.0001). Furthermore, we have found an intense significant relationship between the total scores of the frequency and severity and some symptoms.** From among the neuropsychiatric symptoms, we could see the strongest relationship in terms of quality of life, depression, anxiety and irritability that is to say these were the symptoms that have been a negative impact on the patients' quality of life. The relationship with cognitive functions seemed weaker than the NPS'ones. **In terms of cognitive functions and quality of life, the correlation factor was only r=0.3 which compared to the neuropsychiatric symptoms in these cases were twice as strong.**

The average IIRS was 45.4 +/- 11.9. **Illness intrusiveness shows a significant increase in relation to the NPI total score (r=0.6, (r2=0.35), ANOVA F (1,129) = 70.07, p <0.0001) and the severity scale and frequency scale,** the illness intrusiveness was growing at the same time with becoming more frequency and severity of the neuropsychiatric symptoms. In terms of some neuropsychiatric symptoms, we could saw the strongest relationship with the illness intrusiveness these are irritability, aggression, motor disturbance

and appetite /eating changes. Regarding the relationship between the cognitive functions and diseases burden we could see a meanly strong connection besides the correlation factor of r=0.5.

Geriatric Depression Scale's score is 8.22+/- 3.59. Based on the scale depression could be probable above 10 points. As the exclusion criterions included the depression in the anamnesis thereby a mild rate has appeared in the average score which was probable a mood symptom as part of NPS. Between the groups there were not any significant difference p=0.46. Between the genders also were not any significant difference. Apart from the fact that the sample' average score has not met with that limit where depression most likely would appear but between the patients there were 62 patients who scored 9 or more points. **These patients' total score was 11.4 that is why 47% of the sample would need treatment for depression.** GDS' score was closely related to the indicator of severity and frequency of NPI depression (r=0.7).

The average ADL-I was 4.13 +/- 1.84. Based on the test's description it meant a mean functionality that is why the patient was able to take care of herself/himself with the help of orderly control and supervision. Between the groups there were not any significant difference. The average ADL-II was 14.5+/- 5.68 which meant moderate functionality. We could also not see any differences between the groups. We examined which one of the symptoms was closely related to the impairment of daily activity the symptoms of cognitive or NPS' one. **Regarding to the results we could see that the impairment of cognitive symptoms was closely related to the impairment of daily activity (r=0.6) than the neuropsychiatric symptoms (r=0.4).**

5.5 Results showing the assessment of the caregiver's distress and neuropsychiatric symptoms

Measured here is the level of caregiver's distress with the caregiver's distress index of NPI test, known as 'distress'. The distress factor's total score: 16.55+/-9.14.
There is not any significant difference between the groups (p> 0.05).

First of all, we surveyed that which one of the NPS meant the biggest burden for the relative. For this, we used the scores of the relatives who developed the given symptom. **The highest scores were given for motor disturbance, hallucinations, delusions, nighttime**

behavioral disturbances, agitation/aggression, appetite/eating and changes, depression, disinhibition, and elation/euphoria.

Also examined is the relationship between the caregiver's distress index and the total score of NPS, as well as the severity and frequency. **The three comparisons showed significantly strong correlations (r=0.98, (r2=0.97), ANOVA F (1,129) = 1531.02, p <0.001), where the more frequent NPS was associated with the most severe distress of caregiver's.**

Below are the correlations between cognitive functions and NPS. **A moderate correlation was seen between the result of the test measuring cognitive functions and the total score of distress (r=0.4, (r2=0.18), ANOVA F (1,129) = 28.5, p<0.001), where greater impairment of cognitive functions was associated with higher levels of caregiver's distress.**

We got the following results about our research hypothesis:

H1: There will be a high prevalence of the NPS present in the Hungarian sample.

Our first hypothesis was confirmed because we have experienced a 100% frequency of neuropsychiatric symptoms in our own sample.

H2: There is a difference in the frequency of neuropsychiatric symptoms in neurocognitive disorders with different etiology.

Our second hypothesis was also proved because we could see that in the case of the dementia of Alzheimer's origin some symptoms were more common and severe such as psychotic symptoms, euphoria, motor disorders, and sleep-wake cycle's disorders but in the case of vascular's origin, the symptoms of mood life were more common and severe. NPS profile of mixed origin diseases was similar to the neurodegenerative origin.

H3: The deterioration of cognitive functions are associated with the severity and the frequency of neuropsychiatric symptoms.

Our third hypothesis was proved by some significant results that are why the frequency and severity of neuropsychiatric symptoms were significant meanly strong related to the impairment of cognitive functions. The results presented that the lower-level cognitive functions have shown some relevant changes in terms of the frequency of the following

symptoms: apathy, disinhibition, irritability, motor disorders, and eating-appetite change and in terms of the severity of the following symptoms: apathy, disinhibition, irritability, motor activity disorder, sleep-wake cycle disorder, and eating-appetite change.

H4: The NPS expressively affects the patient's quality of life and illness intrusiveness.

In the case of our fourth hypothesis, we could see a significant meanly strong relationship between quality of life and neuropsychiatric symptoms thereby the NPS significantly contributed to the changes in patients' quality of life. This connection was found twice as strong as the effect on the quality of life of cognitive symptoms. We could see a similar results about the illness intrusiveness.

H5: The effects of the NPS will have an important impact on caregivers' burden, and this is stronger than the effects of the cognitive functions.

Our fifth hypothesis was also significantly proved because based on our research's results that the neuropsychiatric symptoms' effect was more than twice strong on the relatives like the impairment of cognitive functions' effect.

6. Discussion

In this study, we examined the frequency and severity of NPS to the patients who have been living at home, and firstly visited the specialist care because they have been suffering from a major neurocognitive disorder. Our sample on average showed a medium severity of dementia. Demographical data (gender distribution: 36.64% male, mean age: 77 years) of our sample was comparable to that of previously examined samples reported in the literature. Based on the 17 scores on average of MMSE result and the 36 scores of ADAS-Cog result that in this case, we have been talking about medium severity major neurocognitive disorder where the patients have been able to take care of themselves but they are also needed some help however, the hospitalization has not required yet.

In our study, the prevalence of BPSD symptoms was 100%, meaning that there was no patient in our sample without at least one NPS. These results are associated with the published data in the literature. The high-frequency rate has also confirmed our initial assumption according to which we should take greater emphasis on the NPS.

The reason for this exceptionally high prevalence rate of NPS may be that in our study the evaluation of the NPS was thorough, was based on a very detailed NPS-specific interview, and that the questions were directed to the patient's primary caregiver. In contrast, most of the studies reporting data on the presence of NPS in patients used either less specific and less detailed measurements, or a different information source (self-evaluation, doctors rating, etc.)

Based on our results, the most frequent NPS were motor disturbance (69.31%), depression (46.21%), agitation/aggression (44.12%), appetite/eating changes (35.03%), anxiety (30.11%), nighttime behavioral disturbances (28.78%), delusion (28.77%), irritability (24.62%), and hallucination (22.72%), whereas apathy/indifference, disinhibition, and elation/euphoria were present in less than 10% of cases. These findings are different from previously reported findings in the literature regarding the prevalence of mood disorder symptoms and the possibly related appetite/eating changes and nighttime behavioral disturbances. A reason for this difference may be that in our study patients with previously diagnosed mental disorders – including major depression – were excluded to avoid overlapping symptom detection (e.g., affective symptoms being present, not due to BPSD but because of a pre-existing mental condition). It could have been an impact on the depression and the apathy's frequency rate because of this it showed a lower prevalence than the previous data. Besides the detailed anamnesis and the relatives' conversation, many problems were revealed which earlier

were not diagnosed as a symptom and it could have been an explanation for the higher prevalence of motor disturbance and appetite /eating changes.

Our findings suggest that NPS as a symptom group requires medical attention because, in line with previous data, the most frequent symptoms in our sample were those that had been already reported as important risk factors for higher mortality rates and early nursing home placement.

As the second objective of this study, we examined whether a specific NPS pattern existed in different types of dementias because during the clinical practice it could be very challenging to separate some dementia forms that is why we wanted to survey the indicators of cognitive functions and neuropsychiatric symptoms of patients who have been suffering from a major neurocognitive disorder. Our results showed that hallucination, motor disturbance, and anxiety were significantly more frequent in AD and MD compared with VD. Brain SPECT confirmed frontotemporal-perfusion abnormality in Alzheimer's patients with NPS. Based on post-mortem data, more neurofibrillary tangles were found in the brain of patients previously showing psychotic symptoms like hallucinations or delusions. This finding indeed connects the presence of these NPS to Alzheimer-specific neuropathology. Thus, psychotic symptoms are less likely to be taken as generalizable NPS in dementia. Our results also showed that in the group of the neurodegenerative etiology the psychotic symptoms have appeared greater frequency and severity than between the vascular patient. The presence of mood disorders such as apathy, irritability, agitation, depression, and euphoria, as well as delusions and disinhibition, have been, however, emphasized in vascular dementia in previous reports

Our results have been shown that not just the dementia subtype has been connected with the frequency and severity of certain NPS but also the stage of cognitive impairment. We used all three types of cognitive functions 'measuring process and these presented a significant relationship with the NPS' total score on the NPI scale and on the BEHAVE-AD scale in addition with the indicator of frequency and severity on the NPI scale. In case of these the cognitive function which is worse, it is able to cause more NPS and make more severe symptoms these are very important information because of the aim to prepare the family and to educate the patient. Nursing's problems are caused because of greatly hard to predict forward what kind of symptoms could appear in the patient's increasingly severe status or what problems the relatives can expect. That is why it is highly important to separate from each other the major neurocognitive disorders' different origin on the level of neuropsychiatric symptoms

to give more help to the relatives caring for the patients. Relatives could prepare better for unexpected situations by describing a more accurate symptom picture thereby in terms of patients could be extended to stay home and could be reduced to stay in a nursing home which would be a huge financial burden for the relatives and social security system, too. Our results were proved that in cases of the patients who could stay at home for a longer period of time, it was a significant positive effected on the patients 'quality of life and on the disease's prognosis. That is why our first aim was to provide it during developing to the modern nursing strategies and in this case, it was essential the accurate knowledge of symptoms.

We also surveyed which ones of neuropsychiatric symptoms especially have been responding sensitively to the impairment of cognitive functions. Because of this, we got a result in which the motor disturbance, which were the most often occurring symptoms and examined by us, have responded sensitively in all three tests in addition, these presented significant relationships with the impairment of cognitive functions. Worse cognitive functions were related to a higher frequency and greater severity of apathy, irritability, nighttime behavioral disturbances, appetite/eating changes, motor disturbances, and disinhibition. In terms of these, we could predict that the more cognitive functions were getting worse the more motor disorders the patients were getting severe in addition many problems could appear like swapping day and night, delusions, more severe appetite problems, intensifying irritability, and apathy.

Interestingly, our findings showed that hallucinations and delusions were related to the etiology of dementia and were independent of the level of cognitive deterioration, whereas apathy, irritability, nighttime behavioral disturbances, and appetite/eating changes were associated with cognitive deterioration and were independent of etiology.

We found two symptoms, motor disturbances, and disinhibition that were both associated with aetiology and cognitive deterioration. Motor disturbances were the most frequent NPS, so it might be an early appearing NPS, especially in AD, whereas disinhibition was one of the less frequent NPS in this sample, thus it may appear in later phases (in severe cases – our sample was on average medium severity), and is typical especially for VD. These findings are in line with previous findings

Neuropsychiatric symptoms have been causing the worse quality of life and pain for both the relatives and patients, too. Both physically and mentally have been affecting greatly negative on the caregivers and relatives. The neuropsychiatric symptoms have made the

nursing's distress increasing and the home care's time reducing. Symptoms have caused high-intensity distress which could be the reason for the early hospitalization. However, these have had a significant cost implication because nursing costs and hospitalization have been cost-increasing factors besides the waiting time was greatly long.

Regarding the previous research's results presented us the severe negative effect of psychotic symptoms and disruptive behaviors for example aggression, agitation, etc. In our own sample, we got different results about the relatives 'burden. Based on our results the biggest burdens as symptoms were motor disturbance, depression, agitation/aggression, appetite/eating changes, delusion, and night-time behavioral disturbances. In some of the previous published studies were born similar results, too. The reason for the differences could be the subjectivity which was mentioned in the literature because the characteristics of the relatives (age, personality, struggling skills, life situation, health condition, etc.) could determine how hard to bear with the symptom. We could see clearly that in terms of the patients and their relatives that different symptoms could be severe. We have seen a really significant relationship between the neuropsychiatric symptoms, quality of life, and illness intrusiveness which are the same as the literature's data in spite of this patients' quality of life and mental burden of disease have been surveyed in a few studies. In 2011 Banerjee and his fellow workers made a study in which the result was found neuropsychiatric symptoms have been getting worse the quality of life three times severe than the impairment symptoms of cognitive functions.

In the study of 2008 which measuring quality of life in case of both patients and relatives they surveyed the quality of life and they made a conclusion that neuropsychiatric symptoms have been reducing the quality of life in terms of both patients and relatives in addition, increasing disease's burden as getting worse the symptoms. These results have confirmed our own study's results in which the patients have had major neurocognitive disorder their quality of life has been quite low but disease's burden has been especially high. Besides we have confirmed in our study that the reason for the mental burden of relatives was the neuropsychiatric symptoms and not the symptoms of the impairment of the cognitive functions.

7. **Summary**

In our research we were looking for the answer how the cognitive functions and neuropsychiatric symptoms had been changing among the patients with major neurocognitive disorder in our sample. Our results - based on a study of naturalistic sample of patients with dementia without treatment - confirmed previous findings in literature on patients with neurocognitive disorder that these were related to the high prevalence of NPS. We have found significant differences in the presentation of NPS within clinical subtypes of major neurocognitive disorder. In addition, we have identified a significant relationship between the level of cognitive impairment and the appearance of NPS.

We also proved the importance of the frequency of occurrence and the severity of neuropsychiatric symptoms among the patients with major neurocognitive disorder. According to our results many problems can occur in the life of patients and their relatives which have a serious effect on the progression of the disease. The first hypothesis of our research – whether it is essential to deal with neuropsychiatric symptoms in patient care - was plainly answered.

The second question - whether in terms of neuropsychiatric symptoms there is any difference between the major neurocognitive disorders of different etiology - had also been answered with significant result. It can be seen that among patients with Alzheimer's dementia psychotic symptoms, anxiety, disorders of motor functions and diurnal rhythm disorders were more common and severe. However, in case of dementia with vascular's origin we reported the prevalence of affective symptoms.

Our third question - whether there was any relationship between the cognitive functions and neuropsychiatric symptoms - also resulted with a significant finding. We could see that due to the impairment of cognitive functions the frequency and severity of neuropsychiatric symptoms were increasing especially in terms of apathy, disinhibition, irritability, motor disorders, eating-appetite change, disorder of sleep-wake cycle and delusion which have confirmed the previous conclusions namely that neuropsychiatric symptoms greatly contribute to the process of hospitalization and the fact that patients get out of the family.

Our fourth question was targeting a relationship between the neuropsychiatric symptoms of neurocognitive disorder and the different indicators of the quality of life. According to our knowledge this was the first study in Hungary with this aim. The necessity of our research was based on the demand for better care and optimal use of resources. If the patient can stay

at home for a longer period of time, this situation might improve the patient's quality of life. This should be the main goal of up-to-date nursing projects, but it assumes the exact knowledge of the expected progression of symptoms. Our results have confirmed that neuropsychiatric symptoms have a significant impact on the patients' quality of life and the burden of the illness, which seemed more intense than the effect of cognitive functions.

Our last, fifth question emphasized the impact of neuropsychiatric symptoms on patients' relatives, which turned out to be twice stronger than the effect of cognitive symptoms. This was the first Hungarian study which calls attention to the importance of neuropsychiatric symptoms since the caregiver's burden and nursing circumstances greatly depend on the frequency and severity of these symptoms.

Most of all, the importance of neuropsychiatric symptoms lies in the fact that these are the main factors in hospitalization and mortality of patients with major neurocognitive disorder. The reason for patient's hospitalization mostly depends on the stress of the caregiver relative. In most of the cases, there is always a neuropsychiatric symptom in the background. The severity of the impairment of the cognitive functions, the type of the disease and the age of the relative are also contributing factors. The patients with neuropsychiatric symptoms often suffer from fear or live-in isolation, beside the rising healthcare costs and increasing mortality and morbidity rates.

The significance of our study relies on the fact that - as far as we know - there has not been any Hungarian research on patients with neurocognitive disorder, where neuropsychiatric symptoms played a main role in the investigation, without observing the effect of a drug intervention. This was the first systematical study to collect information about the neuropsychiatric symptoms among Hungarian patients who have been suffering by neurocognitive disorder.

Moreover, we have not examined only the patients but also their family members who live with them. Since we suppose that the disease itself has an impact on both the patient and their family, the patients and their relatives were examined together during the study. It was an essential aspect in terms of our methods that we controlled each one of them by another method made for a similar purpose - whether we consider the cognitive functions or the neuropsychiatric symptoms - this is how we tried to eliminate those faults which can come from the subjectivity of neuropsychiatric symptoms, thereby we were able to survey a total of 33 neuropsychiatric symptoms besides searching for a wider cognitive function.

Our results indicate that while taking care of patients with neurocognitive disorder one has to focus more on this syndrome because the most common symptoms were the most sensitive for the impairment of cognitive functions and these cause the largest mortality risk and hospitalization. In addition, our results have also confirmed that as compared to cognitive symptoms neuropsychiatric symptoms had more than double impact on the mental burden of the caregiver.

As a result of our research, we highlight the importance of family involvement and education during the early diagnostic steps for solution of the nursing problems in care of major neurocognitive disorders. We have presented a more detailed picture about the higher frequency of occurrence and the types of symptoms, which was due to the assessment of symptoms performed in cooperation with the relative (a technique desirable for use in patient care). Our findings are preliminary, and future studies are necessary for the detailed understanding of these relationships. A study of non-cognitive neuropsychiatric symptoms in relationship with different types of Major Neurocognitive Disorder is recommended. That could help doctors during the diagnosis, in giving information to the patients and their relatives, moreover in education about the progression and outcome of the disease. A foreseen course of the illness can help caregivers to prepare against future challenges. As a result, the length of home care can be longer delaying the need of patient's referral to a nursing facility.

8. Fundings

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List of publications related to the dissertation

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List of other publications

3. Sárváry, A., **Laczkóné Majer, R.**, Jávorné Erdei, R.: Lelki egészség Nyíregyháza lakosai körében = Mental Health among residents of Nyíregyháza.
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4. Bencze, J., Simon, V., Bereczki, E., **Laczkóné Majer, R.**, Varkoly, G., Murnyák, B., Kálmán, J., Hortobágyi, T.: A Lewy-testes demencia klinikai és neuropatológiai jellemzői.
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