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SUMMARY

Supervisor:
PROF. UNIV. DR. TUDOR UDRIȘTOIU

Ph.D. Student:
DR. MOȚĂȚĂIANU (DRAGAN) MARIANA

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EPIDEMIOLOGIC AND CLINICO-EVOLUTIVE PARTICULARITIES OF DEMENTIAS

Supervisor:
PROF. UNIV. DR. TUDOR UDRIȘTOIU

Ph.D. Student:
DR. MOȚĂȚĂIANU (DRAGAN) MARIANA

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BACKGROUND

INTRODUCTION. THE IMPORTANCE OF THE PROBLEM

Dementia has become a major public health issue, a global threat. A report by Alzheimer's Association from 2013 estimates 35.6 million cases of dementia in 2010, 65.7 million in 2030 and 115.4 million in 2050, while the worldwide occurrence is 7.7 million patients, *i.e.* one new diagnosed patient every four seconds (1).

There is a deficit of actual epidemiologic information regarding the occurrence and prevalence of dementias, considering the fact that the acquired data are based only on diagnosed cases, with many patients remaining undiagnosed. According to data supplied by the Romanian Alzheimer Society at the National Alzheimer's Conference 2013, the number of people aged over 65 years old has increased, in our country, to 20.5 % of the population in 2011, and the number of people suffering from dementia is estimated to be around 350,000, of which 150,000 have been diagnosed and only 5,000 have been treated.

The aim of this work is to increase awareness of colleagues, authorities and the target-population (the patients and their families), regarding the proportions and damages caused by this disease. Another issue of concern analyzed within this study is the fall in the age of the people developing early stages of the disease to under 60 years of age, with a few cases under 50 years of age.

CHAPTER I. DEMENTIA IN PSYCHIATRY

1.1. Dementia as a concept

The concept of dementia was interpreted in different ways over the years, in accordance with scientific data, diverse psychological and medical trends, and social and cultural mentalities at a certain time. According to ICD-10 (International Classification of Diseases, 10th Revision), dementia is defined as "'a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capability, language, and judgement". In certain cases, consciousness is altered and the deterioration of cognitive functions can be accompanied or preceded by the deterioration in emotional control, changes in social behavior and motivation (2). According to epidemiologic studies, 50–60 % of those who suffer from dementia have Alzheimer's dementia, 10–30 % have vascular dementia, while 10–15 % show mixed types, both vascular and Alzheimer's. This results in 75 % of the cases being the main two types of dementia. The remainder encompasses the other types of dementia: dementia with Lewy bodies, Parkinson's disease, other types of dementia associated to neurodegenerative conditions, inflammatory or infectious diseases, neoplasia, and metabolic diseases (3).

1.2. Epidemiologic data

Alzheimer's dementia has a complex determinism: genetic, vascular, toxic, infectious, traumatic, inflammatory, metabolic and neurobiochemical. The theories behind the pathogenesis of the disease and their interpretation have represented the starting point for the discovery of specific medications, bringing in solid arguments for a precocious treatment. At the moment, it is

a fact that with physiological aging, there is a progressive decrease of activities of neurotransmitters, receptors and enzymatic systems, and, at the same time, there is a progressive loss of neuronal mass. The decrease of cholinergic activity, along with mnesic decline is at the core of the "cholinergic hypothesis" in Alzheimer's dementia. Further aspects of this decrease are the cortical cholinergic deafferentation, the decrease in the activity of choline acetyltransferase (the enzyme involved in the synthesis of acetylcholine), and the lower activity of muscarinic receptors. Another argument is the therapeutic one; administering inhibitors of acetylcholinesterase (IAChE) improving cognition.

1.3. Etiopatogenic aspects

A correct diagnosis of the disease is based on corroborating several pieces of data: clinical and psychological, using different assessment and paraclinical scales, imagistic data, usual analyses and respecting the international diagnosis criteria. Regardless of the etiological substrate, the main reason consists of a decline in superior psychical functions, cognition, loss of intelligence, and loss of personal essence, all of which should be sufficiently severe to cause a "clinically significant distress or impairment in social, occupational, or other important areas of functioning", other than the regular decline that occurs with aging, according to DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders ed. IV Revised) (4). Cognitive functions can be quantified using neuropsychological questionnaires. The MMSE (Mini Mental State Examination) (5) is the most commonly used tool in medical practice.

1.4. Diagnosis. Nosologic approaches

Current therapy has three objectives: prevention, symptom amelioration and intervention in the clinical evolution. Symptomatic medication, also known as anti-dementia or procognitive medication, has drawn most of the attention, and it is based on **cholinergic therapy**, with numerous clinical studies. According to therapeutic guides (Băjenaru, Tudose, 2007) (6), the election therapy of the cognitive deficit is assured by drugs with specific action: inhibitors of acetylcholinesterase (IAChE), donepezil and galantamine; inhibitors of acetylcholinesterase and butyrylcholinesterase (IBuChE), rivastigimine; glutamatergic modulators (of NMDA receptors), memantine.

1.5. Therapeutic management in Alzheimer's dementia

Along with procognitive therapy, for the treatment of dementia, the therapeutic intervention on non-cognitive disorders is highly important. These disorders include: depression, psychotic disorders, behavior changes, psychomotor agitation. Therapeutic intervention is performed using antipsychotic medication, antidepressants, mood-stabilizing drugs and sedatives.

PERSONAL RESEARCH

CHAPTER II. WORK HYPOTHESIS. OBJECTIVES. METHODOLOGICAL COORDINATES

2.1. Work hypothesis

Results from clinico-epidemiological studies suggest relationships between the debut and evolution of dementias, with individual characteristics, such as the age of the patient at debut, or the precocity and quality of therapeutic interventions. On another hand, the presence of comorbidities could negatively influence the evolution and prognosis of the disease, which means diagnosis and treatment of these comorbidities becomes the main focus. Further research on the relationship between dementia–individual characteristics–comorbidities could lead to the discovery of new predictive factors for evolution and ameliorating therapeutic strategies.

2.2. Aims of this research

- Studying the characteristics of patients suffering from dementia, with or without psychiatric comorbidities, under procognitive treatment.

- Highlighting relationships between the presence of psychiatric comorbidities and the evolution of cognitive deterioration.

- Highlighting relationships between independent variables (gender, age, education, marital status, residence area, diagnosis, treatment) and the dependent variable, cognitive deficit, measured *via* MMSE scores, in the evolutionary stages of dementia.

2.3. Methodological coordinates

Retrospective study, of a batch of patients, N=560, diagnosed with dementia according to ICD-10 criteria, accounted for by the Mental Health Center (CSM) for Adults, Craiova, over a time frame of 66 months, between January 1, 2008 and June 30, 2013.

By applying inclusion and exclusion criteria, the **main batch**, **N=560**, was constructed for patients diagnosed with Alzheimer's dementia and mixed dementia. This was divided in two **sub-batches**: **N1=332** patients suffering from dementia and psychiatric comorbidities, and **N2=228** patients suffering from dementia, without psychiatric comorbidities at the time of diagnosis.

The Mini Mental State Examination (MMSE) scale was used to monitor the evolution of cognitive deterioration, at the beginning of the case study, after one year and at the end of the case study.

Data recording was performed electronically, using a protected file, and the interpretation of results did not include data which would lead to identifying the patients.

2.4. Statistics software

For the interpretation of data, Microsoft Excel® (Microsoft Corp., Redmond, WA, USA) was used, along with the XLSTAT suite for Microsoft Excel® (Addinsoft SARL, Paris, France) and SPSS Statistics 20.0 developed by IBM (IBM Corporation, Armonk, NY, USA).

CHAPTER III. RESULTS

Of the batch analyzed, N=560, 58.57% are women. Based on age, over 4/5 of the cases are aged between 50 and 79, according to the literature (7, 8). Furthermore, half of the patients have ages between 70 and 79. Patients in the sub-batch N1, suffering from psychiatric comorbidities, have benefitted from a precocious diagnosis, 26.81% being diagnosed before the age of 60, while in sub-batch N2, only 3.51% were diagnosed before the age of 60.

For the entire batch under analysis, the highest percentage is represented by patients with primary school studies (55.51%), whereas university degrees have fewer representatives (8.04%). Based on gender, statistically significant differences were observed according to educational levels, with women subjects being dominant for primary school and high school studies, whereas male counterparts predominate for vocational and university studies.

More than half of the patients are married, specifically 56.25% of the patients, while the widowed ones represent 39.82% of the total, and the single patients only 3.93%. There is a highly significant difference between the distribution according to marital status of men and women: male patients are married in 75.86% of the cases, while female patients are widowed in over 50.00% of the cases.

The patients from urban areas represent 58.93% of the batch. The lower economic level in the rural area and the mentalities specific to that area regarding ageing, behavior changes, cognitive decline and physical degradation, are considered to be normal at older ages, or are considered to relate to external factors: low educational level, alcoholism. Regarding differences in distribution on residence areas between the two genders, there is no significant difference, even if the women from urban areas represent a higher percentage than men (61.28% *versus* 55.60%).

Within this study, an astonishing percentage is represented by patients with family support (92.86%), which proves that most patients live with their children or life partner, and others have the possibility of caregivers. Institutionalized patients represent the remaining 7.14%, and they reside in private care homes.

In batch N, a significant percentage (78.93%) are patients diagnosed with Alzheimer's disease, while the remaining 21.07% of the cases suffer from mixed dementia, which confirms the previously reported results (9, 10). Percentagewise, women are more affected by Alzheimer's dementia (82.01% *versus* 74.57%), while the gender distribution for mixed dementia is nearly equal. There are higher percentages for patients diagnosed with Alzheimer's disease for all age groups. Thus, for those in their sixth decade, the number is four times larger than those diagnosed with mixed dementia, while the number those aged over 80 diagnosed with Alzheimer's dementia is five times higher. In sub-batch N1, the number of cases with mixed dementia is 19.28%, which suggests that patients with psychiatric comorbidities at the debut, who attended a psychiatric consultation for symptomatology and not for cognitive decline, do not appear to have an important subjacent vascular composition, while for patients in sub-batch N2, with mixed dementia, the percentage is 23.68%, which suggests the existence of a vascular component.

All of the patients included in the study underwent procognitive treatment, specifically 7 categories of procognitive therapy, which was either monotherapy, or the combination of two drugs. A major percentage in this is represented by inhibitors of acetylcholinesterase, in monotherapy (63.75%), while combinations with it are another 22.68%. Memantine represents 13.57%, its prescription being correlated with moderately severe and severe dementia.

The associated treatment was divided into five categories, according to intervention on psychiatric comorbidities and non-cognitive symptomatology, or as procognitive therapy aid (brain trophic factors).

It has been observed that 41.96% of the patients in the study batch are taking antidepressants, followed closely by patients under treatment using brain trophic factors (40.18%) and antipsychotic drugs (38.21%). As expected, the percentage of patients in sub-batch N1, who are under treatment using antidepressants, is 63.25%, followed by patients under treatment using antipsychotic drugs (45.48%) and patients being treated with brain trophic factors (43.67%). Patients in sub-batch N2 have brain trophic factors as their main drugs (35.09%), followed by antipsychotics (27.63%), which is in accordance with moderately severe and severe dementias from debut, which require associated treatment.

For sub-batch N1, the percentage of patients suffering from depression as comorbidity is 71.38%, followed by delusional disorder (20.18%) and organic personality disorder (6.63%).

The assessment of cognitive decline was performed at the beginning of the case study, after one year and at the end of the case study. We distributed the patients within the known evolutionary stages of dementias according to their MMSE scores at the three assessments. A statistical analysis of MMSE test scores was performed, determining their averages and standard deviations. The average MMSE score for each of the three assessments was 16.88±4.98% (beginning), 15.17±5.58% (after one year) and 14.24±5.46% (end). At the beginning of case studies, there were 26.43% of patients suffering from mild dementia, which drops for the next two assessments, with some of these patients being in moderate or severe stages of dementia. There is a steadfastness of patients in moderate decline, due to evolutionary dynamics under treatment. 10. 54% of patients were in the severe stage from the beginning and the number of patients in the severe stage has doubled during the study, either because of mediocre evolution from the very beginning, or because of progredient evolution of cognitive decline from the mild and moderate stages. A progressive decrease in the number of patients of both genders being in the mild stage of the disease has been recorded for the three assessment times and a progressive increase of those in the severe stage of the disease was observed for the intermediate assessment and the final one. For the final assessment, cognitive decline is obvious, even though patients are under permanent procognitive treatment. Analyzing each age group separately, we found significant and very significant differences between the three assessment times, except for average values between the intermediate assessment and the final one for patients aged 50 or less.

CHAPTER IV. DISCUSSION

According to the last census (2011), the Dolj district has 660,544 inhabitants, of which 51.20% are women and 48.80% are men. Considering the 1761 cases of dementia recorded by CSM Craiova, there is a prevalence of 0.26% in 2012, 59.74% of the patients being women. The studied batch, N=560, is representative for the population of the district.

In sub-batch N2, there is a higher percentage of women, in comparison with sub-batch N1, suggesting that female patients with a cognitive debut are higher in numbers, whereas the men in sub-batch N1 represent a greater percentage than those in sub-batch N2. One explanation could be debut *via* psychiatric comorbidities, which is more evident than cognitive debut due to behavior and mood changes, which are easy to observe by the entourage. For both sub-batches there were no significant differences between genders for all three assessments between MMSE scores registered. There is a progressive decrease in the number of patients, regardless of gender, in the mild stage of the disease over the three assessment times and a progressive increase in number for those in the severe stage, for the latter two assessments; this was more obvious for female patients.

In batch N, the highest percentage was represented by the age group 70–79, specifically 41.07%. The percentage of patients under 50 years of age is very small for sub-batch N1 and there are no patients under 50 years old in N2. However, in sub-batch N1, there is a higher percentage (26.81%) for "younger" patients (aged 50–69), which suggests that patients suffering from psychiatric comorbidities, due to the mood and behavior changes, turn up earlier to consultations and benefit from diagnosis and precocious start of the therapy. It was observed that patients in sub-batch N1, with ages under 50, had an inferior evolution in comparison with patients aged 50–59 and 60–69, even though they initially had higher average MMSE scores; this could relate to psychiatric comorbidities such as depression and delirium, which are more frequent for this age group. We observed highly significant differences between age group, by analyzing each assessment time, and also average MMSE scores. In sub-batch N2, it was observed that a "strictly" cognitive debut is absent for patients with ages below 50, there are few patients aged 50–59, and higher percentages were observed for the 60–69 age group, while nearly half of the cases in this age group belong to the 70–79 age group. It is observed that initial MMSE average values, according to age groups are relatively constant until the age of 79, with smaller score values being recorded for those aged over 80. For the final assessment we observed a progressive decrease of average values. At the starting point of the case studies, there are significant differences between MMSE scores recorded on age groups, while for the other two assessments, they are highly significant. Comparing the scores obtained for the three assessments, for both sub-batches, we observe an inverse correlation between age and average MMSE scores, which implies that MMSE scores decrease with age.

In sub-batch N1, patients with high school, vocational and university studies have a better evolution than the others. It was noted that patients who belong to the three educational levels mentioned above are more numerous in urban areas, and the results obtained can be correlated with their involvement in intellectual activities, access to information and a higher economic level. There is an upward slope for the intermediate assessment (one year in the study) for those who only attended primary school and/or vocational school. In sub-batch N2, patients who went to vocational schools or universities obtained better MMSE scores, while patients with primary school studies only, had poorer results for memory tests and a cognitive decline similar to those who had different educational levels. Comparing average MMSE scores, according to

educational level, we observed highly significant differences between the different categories, for each assessment time.

We identified a significant difference between marital status of sub-batches N1 and N2. Patients in sub-batch N1 are mainly married (60.48% *versus* 49.56% in N2), while patients in N2 are mainly widowed (48.68% *versus* 33.73% in N1). Single or widowed persons are more exposed to dementia as they age (11, 12). In our batch, the widow status significantly associates with precocious dementia and unfavorable evolution of cognitive decline. For both sub-batches, we observe that married, divorced or single patients have obtained better MMSE scores for all three assessments. We identified highly significant differences between average scores at the initial and final assessments, as well as highly significant differences between average MMSE scores calculated for the same category of patients.

For both sub-batches, it was observed that patients from urban areas recorded better MMSE scores for all three assessments, which can be explained by a higher educational level, a better economic status, better knowledge about the disease, precocious diagnosis and better medical services. By comparing average scores recorded for the three assessments, we observed highly significant differences between the residence areas at all assessment times. There are significantly lower values between the two residence areas for the one-year assessment and the final one.

We proved the existence of highly significant differences between average MMSE score values for patients in sub-batch N1, with psychiatric comorbidities; these differences are also found between scores for patients suffering from depression disorder and organic personality disorder, who obtained higher MMSE scores, in comparison with patients diagnosed with delusional disorder, for all three assessment times.

It was observed that over three quarters of the patients in the entire study batch were diagnosed with Alzheimer's dementia. For the initial assessment, 48.57% of the patients were in the moderate stage of the disease, while for the other two assessments, high values of percentages for the moderate stages were still present (MMSE score = 20–10), by negative migration of patients from the mild stage of the disease.

If only 7.86% of patients were in the severe stage of the disease at the initial assessment, their number doubled for the one-year assessment, their number being three times higher for the final assessment. This proves the progredient evolution of the disease over time, even though the patients are under procognitive therapy. Patients with mixed dementia (21.07%) have shown the same evolution. There is a higher average value of MMSE scores, statistically significant, for patients suffering from Alzheimer's dementia, in comparison with those diagnosed with mixed dementia for all three assessments.

There are highly significant differences between average MMSE scores and procognitive treatment categories for both sub-batches. We noticed that patients requiring memantine or anti-dementia associations have a lower MMSE score starting from the initial assessment and a poorer evolution, overall. We observed that, for each therapy, significant differences between the three assessments, the differences being more obvious for those under treatment using memantine or associations. For sub-batch N2, we noted significant differences between all three assessments, except for those treated with galantamine, where the only differences were between the first and last assessment.

CHAPTER V. CONCLUSIONS

1. The prevalence of dementia, recorded in 2012, in the Dolj district, is 0.26%, with a tendency to increase and predominant for women (59.74%)
2. In the studied batch, women represent 58.57% of the patients, patients with ages over 60 years, 82.68%, while the highest percentage for age groups is 41.07% for those aged 70–79.
3. The presence of psychiatric comorbidities (57.50%) is related to the precocity of the clinical debut; 26.81% of patients suffering from psychiatric comorbidities were registered before they turned 60, in comparison with only 3.51% of those without comorbidities. Also, the presence of psychiatric comorbidities relates to a lower survival rate (10.54% over 80 years old, *versus* 30.26%).
4. If educational level had no significant correlation with the presence of the disease, the widowed status represents 39.82% of the batch and is significantly correlated with the presence of the disease. Differences recorded according to residence area, which are statistically significant, cannot be interpreted *per se* due to very different addressability and accessibility, both from a cultural point of view and because of real deficiencies of psychiatric assistance over the studied geographical area.
5. Alzheimer's dementia represents 78.93%, having a significantly higher percentage, regardless of gender, age, educational level or marital status, psychiatric comorbidities, or social support. The majority of patients (92.86%) benefit from family support.
6. Procognitive treatment was based on monotherapy (IchE, 63.75%, and memantine, 13.57%), or associations (IchE and memantine, 22.68%), while associated treatment was dominated by antidepressants (41.96%), drugs for brain trophic factors (40.18%), antipsychotics (38.21%), and sedatives (21.43%), all of these being prescribed for comorbidities.
7. The average MMSE score for the entire batch for each of the three assessments was 16.88±4.98%, 15.17±5.58% and 14.24±5.46% respectively, all within range for moderate dementia.
8. The aggravation of cognitive deficit does not differ significantly between genders, but it correlates significantly with age (over 70 years old).
9. Unfavorable evolution of cognitive deficit significantly correlates with the widowed status and is inversely correlated to the married/single status.
10. The severe stage of dementia had an increasing percentage, starting from 10.54% of the patients at the initial assessment, and increasing to 20.54% at the intermediate assessment, reaching 28.04% at the final assessment, while the mild stage dropped from 26.43% to 18.57% (intermediate assessment) and 15.18% (final assessment). These differences were statistically significant.
11. A relationship between educational level and the evolution of cognitive decline cannot be established, even though there are significant differences favoring those with university, vocational or high school studies against those with primary or secondary school studies.
12. The evolution of patients suffering from Alzheimer's dementia was highly significant, and superior for those with mixed dementia for both the intermediate assessment and the final one.
13. The precocity of the treatment was significantly correlated with a better evolution: the sub-batch suffering from psychiatric comorbidities, 34.94% suffering from mild dementia

at the time of the first assessment and having an average MMSE score of 18.20, and the sub-batch having no psychiatric comorbidities, 14.04% suffering from mild dementia at the time of the first assessment and an average MMSE score of 14.96. During the final assessment, 20.48% were in the severe stage, with an average MMSE score of 15.45, *versus* 39.04% and an MMSE score of 12.48.

Positive factors significantly associated with the evolution of cognitive deficit were: married status, Alzheimer's dementia and the precocity of treatment, while negative factors were: ageing, widowed status and mixed dementia.

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