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ABSTRACT

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EFICIENCY OF ACETYLCHOLINIC ACTIVATORS IN CORRECTING COGNITIVE DEFICIT IN ALZHEIMER DISEASE

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KEY WORDS: Alzheimer disease, cognitive decline, early onset, pro-cognitive treatment, risk factor

INTRODUCTION

Alzheimer disease, a degenerating illness of the brain, determines throughout its evolution the decline of cognitive functions and the progressive deterioration of personality, associated with behavioral disorders, an increasing concern being that the onset of the disease was established steadily at younger ages.

Numerous studies highlighted that approximately 50% of over 65 years old population presents the risk of developing a cognitive invalidating disorder [1], while a meta-analytic study proved that the great majority of degenerative dementia cases are [2].

The onset of cognitive decline, as biological process, is continuous and slow, thus making it difficult to appreciate whether it's genetically determined, by the intervention of environmental factors or it is a consequence of their interaction. The research in this field showed a significant decrease of neurotransmitters, receptors and enzyme systems, central cholinergic deficits being well documented in Alzheimer disease. We underline the outmost utility of early neuroprotective, individualized intervention, based on complex and correct evaluation, with a most realistic interpretation of the correlation between clinical symptomatology and social and human implications, without neglecting ethical aspects, patient's dignity and rights.

The pathological expression of Alzheimerdisease is defined by a notable increase of the age related changes, although without excluding the possibility for normal aging and that this degenerative disease of the nervous system could be due to a common denominator, expressed by the alteration of certain pathways. The ability of the protective systems depends on certain neuro-trophic factors [3], the initiation of these disorders being the potential result of different etiologic factors (toxic, viral, immunologic) that act either on specific neuro-trophic determinants, or on their receptors.

GENERAL BACKGROUND

Currently it is known that Alzheimer disease is etiologically heterogeneous and that various causes may lead to different clinical-anatomic-pathologic relationships, including clinical manifestations, risk factors and response to pro-cognitive and comorbidities therapies are influenced by this heterogeneity.

The Alzheimer disease diagnosis is clinical, based on careful examination and anamnesis, and investigations like computer tomography and laboratory tests are important in establishing specific etiology, but are not relevant for the diagnosis per se, the etiology being suspected on clinical basis in most cases. The vascular dementia rates

second regarding the prevalence in the majority of studies, even though the interpretation should be reevaluated in order to make sure how much the vascular disorder itself may cause dementia. There are several cases of mixed dementia, Alzheimer and vascular, in this case the vascular disease aggravating the dementia symptoms. Some cases of dementia can be prevented, for example the toxic and the infectious dementia, but once there was structural damage to the brain, the dementia caused by these illnesses becomes permanent.

Illnesses that can simulate dementia include situations when the treatment can eliminate the dementia symptomatology, but the dementia will not disappear under pro-cognitive therapy, the difference between the two being the swiftness of the improvement and the high rate of complete recovery of cognitive functions under treatment. The distinction between reversible and irreversible dementia is undoubtedly important for the correct information of the family on what to expect from the evolution of the disease, for the evaluation of the necessary and available support and for preparing the family to accept the progressively deteriorating evolution of the patient's mental functions.

Current pro-cognitive therapies are mainly substitutive, various molecules being tested, in order to correct cholinergic deficit at presynaptic level through acetylcholine precursors, at synaptic level by acetyl-cholinesterase inhibition, as well as postsynaptic level, stimulating the post-synaptic receptors by agonists of muscarinic receptors, studying also the agonists of nicotinic receptors.

Out of the various cholinergic molecules lacking hepatotoxicity, rivastigmine is a dual, carbamate type, acetylcholinesterase inhibitor with cerebral selectivity and of butyryl cholinesterase, that could facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by fully functional cholinergic neurons, with improvement effect on cognitive deficits that are cholinergically mediated. There is proof that cholinesterase inhibition can slow the creation of fragment of amyloidogenic-amiloid precursor (APP), fragments forming amyloid plaques, involved in the fizio-pathology of Alzheimer disease. The recommended initial dosage is 1,5 mg twice per day, increased to 6 mg/day after one month, under condition of lacking adverse effects (nausea, vomit, abdominal pain, inappetence). The release of the patch form of rivastigmine leads to the almost total decrease of such gastric adverse reactions. Donepezil, a reversible inhibitor of acetylcholinesterase at central level, has been considered for the last 10 years as a first line medication for the treatment of cognitive disorders, its positive effects being observed after administration of 10 mg/day for a period of 40 weeks.

SPECIALISED PART

The data supplied for the fundamental and clinical research suggests the existence of relationships of constants and variables of the person, disease and therapeutic interventions with the evolution and maintaining the adaptative potential of the patients with Alzheimer disease, the interpretation of such relationships having the potential to lead to favorable consequences for the patient and his family, in the sense of improving the cognitive deficit, as well as the predictability of the therapeutic results depending on the social demographic and cardiovascular risk factors.

RESEARCH OBJECTIVES

The primary objective of the study was represented by identifying the correlations between early diagnosis and the quality of evolution for Alzheimer disease under treatment, while the secondary objectives considered the identification of clinical evolutive and therapeutic risk factors in Alzheimer disease, as well as underlining the role of cardiovascular factors in the evolution of patients with Alzheimer disease.

METHODOLOGIC COORDINATES

The retrospective study of a lot of cases diagnosed with Alzheimer disease, in the records of the Clinical Hospital for Neuropsychiatry Craiova (Clinic I and Clinic II Psychiatry, Neurology Clinic, Mental Health Centre), in the interval between 1st of January 2006 – 31st of December 2010, patients included in the study group following the use of ethical norms regarding informed consent and safekeeping of confidentiality over personal data.

WORK GROUP

Upon applying the inclusion and exclusion criteria, the work group N=418 was formed of patients diagnosed with Alzheimer disease, admitted in the Clinical Hospital for Neuropsychiatry (Clinic I and Clinic II Psychiatry, Neurology Clinic, Mental Health Centre) over a period of five years (1 January 2006 – 31 December 2010).

STATISTIC INSTRUMENTS

For data processing, the software used was Microsoft Excel (Microsoft Corp., Redmond, WA, USA), together with XLSTAT for MS Excel (Addinsoft SARL, Paris, France) and software IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA). The information obtained was stored in Microsoft Excel files, then statistically processed, aiming at analyzing the relations between patients clinical and paraclinical data.

RESULTS

In the studied group, the figures showed that the number of patients diagnosed with Alzheimer disease was higher for men, statistically significant compared to women (243 versus 175). For the group N=418 the figures showed that the percentage of patients with Alzheimer disease increases as age grows. The most cases of patients are in the age group 65-74 years, 158 cases (37,8%) followed by age group 75-84 years, 151 cases (36,1%). Another result showed that in urban environment the higher percentage is represented by patients with average education level (65,13%), followed by the patients with higher education (26,05%). On the other hand, in the rural area, the prevalence lies with the elementary education level (51,11%), and the patients with higher education have the lowest percentage (8,33%).

In lot N=418 it was observed that for most of the patients the treatment was initiated in the first 6 months from debut (171 patients – 40.91%). A smaller number of patients, 60 cases (14.35%), was diagnosed and treated in the interval between 13 and 36 months from onset of clinical symptomatology. An almost equal percentage is represented by cases diagnosed and treated in intervals of 7 – 12 months (93 patients), respectively over 36 months (94 patients).

The clinical evolution was determined depending on the evaluative moments, to which MMSE scale was applied to determine the severity of cognitive deterioration:

- M0 (inclusion in the study);
- M1 – 12 months;
- M2 – 24 months;
- M3 – over 24 months

Statistical analysis was performed on the values obtained at the MMSE test, determining the averages and standard deviations. Averages were calculated at M0, M1, M2 and M3 for lot N=418, for the light form of disease (subgroup A), the moderate form

(subgroup B) and the severe form (subgroup C). For the moderate form, averages were calculated depending on the moderate light form (subgroup B1) and moderate severe form (subgroup B2).

Analysis of medication therapy depending on social demographic factors

The clinical evaluation was made depending on the type of treatment administered, assessment of clinical symptomatology evolution given the modification of values obtained from running MMSE test. It was considered improvement an increase of obtained values of up to 3 points, while decrease in values was interpreted as unfavorable evolution. A constant reference of MMSE values was interpreted from clinical point of view as stationary evolution. The administered treatment was donepezil, rivastigmine, rivastigmine patch or associated treatment.

DISCUSSIONS

The differences in the incidence of Alzheimer disease depending on patients gender can be also explained by the higher educational level of men compared to women, especially in different social-cultural contexts (religious and cultural constraints, leading to a lower accessibility of women to education), highlighting an inverse ratio between education level and prevalence of Alzheimer disease. In our study, the smaller number of patients from rural area is correlated with the lower education level (51,11% - elementary studies, compared with 8,33% - higher education), that determines in its turn a lower awareness of the importance and implications of the disease, resulting in a lower rate of diagnosis, while in the urban area the prevalence lied with average education (65,13%) and higher education (26,05%). The influence of the cultural factor on the diagnosis of Alzheimer disease is reflected by the interference between cognitive disorders and daily activities of the patients in urban area, predominantly of cognitive tasks, that amplifies the possibility of early recognition of the symptomatology of the disease, a phenomena that is observed late in the rural area and does not influence the decision for presenting to specialized consult. In the study lot, the rural residence is thus highly correlated statistically ($p<0.01$) with the late moment for treatment initiation, the interval between treatment initiation and real onset of the disease, as well as with therapy continuity.

A statistically significant correlation was observed between analyzed periods from onset and age groups of patients from studied lot, N=418. The younger patients, from the age groups 35-44, 45-54 and 55-64 reported to the doctor in the first 12 months from

clinical onset of the disease, which may be explained by awareness over cognitive disorders manifested at a more socially active age. Age represents a major predictive element for the evolution of patients with procognitive treatment, as it is demonstrated in a study where patients under 75 years had at the treatment initiation moment an average value of MMSE score = 5,3 for those treated with donepezil and 15,2 for those treated with rivastigmine, and those with ages over 75 years had average MMSE scores =15,1 for both types of therapy. The improvement of MMSE score after two years of therapy depended on the age of the patients in the study, those under 75 years showing an improvement of 3,4 points in treatment with rivastigmine respectively 3,8 in treatment with donepezil, compared to patients with ages over 75 years who had an improvement of 2,0 points in those treated with rivastigmine, respectively 1,5 in the group treated with donepezil. Still the differences are not statistically significant, being able to consider that the lot had a stationary evolution, the evolution differences after the treatment being apparent by analysis of the age risk factor, under the condition that the two medication have similar efficiency. [4]

The civil status of the patients is another important factor influencing the presence with the doctor as quickly as possible after noticing cognitive disorders. Statistical data is significant for the studied lot, with the highest percentage from the patients treated in the first 6 months from onset being married people (51,92%) for whom there is family support, while from the group of patients treated at over 36 month from onset, the majority of 43,59% came from the widowed patients, who probably were in an emotional state of neglecting the symptomatolology. A study including 3675 patients with ages of over 65 years followed the risk of Alzheimer disease incidence at 1, 3, respectively 5 years depending on marital status, the categories being: widowed, unmarried, divorced or separated and married. A relatively increased risk was observed in the unmarried patients compared to married patients to develop Alzheimer disease. [5]

Therefore, we can conclude that setting the diagnosis and initiating the treatment as early as possible to the clinical onset of the disease, for a better therapeutic efficiency, is statistically significantly influenced by the education level, residence environment, but also family status.

Administration of procognitive treatment in the first 6 months from real onset of the disease lead for the studied lot N=418 to a percentage of 87,72% of cases with favorable evolution at one year of treatment, while initiation of treatment after 3 years from debut was associated with unfavorable evolution. Depending on the analysis of values obtained

after using MMSE tests upon inclusion of patients in the study (M0), at 12 months of treatment (M1), after 24 months of treatment (M2), respectively at over 24 months of treatment (M3), the statement can be made that in total lot N=418, the evolution was stationary, while cases with light form (subgroup A) had a favorable evolution, those included in moderate light form (subgroup B1) had a stationary evolution, and the patients with moderate severe form (subgroup B2) and the severe form (subgroup C) had an unfavourable evolution. Thus, the earliest initiation of treatment is very important for a better further protection of the cognitive function.

No certain or statistically significant relation between the type of administered medication (donepezil or rivastigmina) and evolution, which demonstrates that the clinical form of the disease is directly responsible for the evolution over time of the disease. This aspect is in accordance with the data from specialized literature that show there is not significant statistical difference between therapy with donepezil or rivastigmina. [6] Other research proved a similar efficiency for the rivastigmine patch form, but with the advantages of reducing adverse gastric reactions presented in the oral administration therapy. [7]

A large number of studies from specialized literature raise the issue of the association between vascular risk factors and Alzheimer disease. Of these risk factors, high blood pressure, low blood pressure, diabetes mellitus, smoking, dyslipidemia seem to play a key role in the pathogeny of Alzheimer disease. [8] [9]

CONCLUSIONS

1. The study group N=418 presented a higher frequency of men (58.13%), compared to women (41,87%), a highly significant statistic difference compared to general population ($p<0,0001$), a prevalence of women in urban environment (62,86%) ($p<0,05$), of married patients (68.66%), as well as of patients with average educational level (54.55%).

2. In the study group N=418 there is a significantly higher weight of men in age groups 45-54 years, respectively 75-84 years, and women in the age group 65-74 years ($p<0,05$), while depending on residence, the urban environment prevaled in age group 65-74 years, and rural environment in age group 75-84 years ($p=3,16 \times 10^{-6}$, $p<0,001$).

3. The earliness in setting the diagnosis was statistically significant influence by the higher educational level ($p=6,64x10^{+7}$, $p<0,001$), by the urban residence environment ($p=1,34 \times 10^{-13}$, $p<0,001$), by married civil status ($p=1,39x10^{-13}$, $p<0,001$) and patients age ($p =4,66 \times 10^{-9}$, $p<0,001$).

4. The evolution of the disease after the first year from establishing diagnosis and treatment initiation was influence by the urban residence environment and the higher education for improved evolution ($p<0,001$), respectively rural environment and elementary studies for stationary evolution ($p<0,001$).

5. Two years from initiating anti-dementia therapy, the unfavorable evolution of the disease was influence by the male gender ($p<0,05$) and educational level ($p =1,50x10^{-7}$, $p<0,001$).

6. The long term evolution under treatment (over two years) of Alzheimer disease in study group N=418 is significantly negatively influenced by the rural environment of patients residence ($p=2,056x10^{-9}$, $p<0,001$) and by the elementary level of education ($p=1,45x10^{-13}$, $p<0,001$).

7. The treatment with rivastigmine represented the first option for the patients from urban area and higher education level, while the donezepil treatment, respectively with other medication association was more frequent in patients coming from rural environment and elementary studies ($p=2,6085x10^{-06}$, $p<0,001$).

8. The therapeutic option is influenced by the interval between the real and apparent debut of the disease, rivastigmine being used prevailingly in the case of patients both with early diagnosis and easier forms of the disease, while for the more severe forms of the disease, with late diagnosis, the anti-dementia treatment was mostly with medication association ($p =2,11 x10^{-54}$, $p<0,001$).

9. The severity of the cognitive deficit throughout the evolution of the disease presented highly significant differences depending on the treatment used (M1 – $p=8,21x10^{-20}$, M2 – $p=7,01x10^{-17}$, respectively M3 – $p=1,00x10^{-22}$), underlining the influence of early initiation of anti-dementia treatment and of the clinical form it was achieved, as well as

the marital status of the patients (M1 – $p=7,06x10^{-6}$, M2 – $p=2,1x10^{-4}$ and M3 – $p=5,24x10^{-5}$), the presence of the family determining the earliness of presentation for specialized consult.

10. The time interval between the real onset and the apparent debut of the disease, represented by the first specialized consult and establishing diagnosis, has significantly influenced from statistic perspective the type of evolution for the disease (M1 – $p=8,13x10^{-66}$, M2 – $p=2,35x10^{-35}$, respectively M3 – $p=3,95x10^{-36}$), the clinical form of presentation representing a major factor for prediction of the cognitive deficit.

11. The cardiovascular risk factors comorbid to Alzheimer disease were represented by high blood pressure (76.79%), dyslipidemia - hypercholesterolemia (72,01%), smoking (34.69%), obesity (32.78%) and diabetes mellitus (16,03%), the association between these amplifying the risk for exacerbation in the evolution of the dementia.

12. The statistic significance of the data obtained confirms the importance of an early determination for the diagnosis of Alzheimer disease, of the initiation of anti-dementia treatment in early stages of the disease, as well as of the management of the social and demographic and associated cardiovascular risk factors, this representing the prerequisites for an efficient therapeutic strategy, that would ensure the patient and his family a better quality of life in the context of a favourable evolution of the disease.

BIBLIOGRAPHY

1. Mahendra, B, 1987. Dementia – a survey of the syndrome of dementia. MTP Press Ltd., Lancaster, 3-5.
2. Gottfries, CG, 1990. Neuropsychopathology of ageing. Psychopharmacology, 86:245-252.
3. Capizzano, AA, Acion, L, Bekinschtein, T, Furman, M, Gomila, H, Martinez, A, Mizrahi, R, Starkstein, SE, 2004. White matter hyperintensities are significantly associated with cortical atrophy in Alzheimer's disease. J Neurol Neurosurg Psychiatr, 75:822-827.
4. Bullock R, Touchon J, Bergman H, Gambina G, He Y, Nagel J, Lane R. Effect of age on response to rivastigmine or donepezil in patients with Alzheimer's disease. Current Medical Research and Opinion 2006, Vol. 22, No. 3 , Pages 483-494

5. C. Helmer, D. Damon, L. Letenneur, et al. Marital status and risk of Alzheimer's disease A French population-based cohort study, Neurology December 1, 1999 vol. 53 no. 9 1953
6. Bullock R, Touchon J, Bergman H, Gambina G, He Y, Rapatz G, Nagel J, Lane R. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. Current Medical Research and Opinion 2005, Vol. 21, No. 8 , Pages 1317-1327
7. Ejaz Nazir, Muhammad Mushtaq, A prospective study on the use of rivastigmine transdermal patch in Alzheimer's dementia in a routine clinical setting Dementia & Neuropsychologia Vol. 4 nº 3 - Jul/Aug/Set de 2010
8. Roman G.C. Royal DR. A diagnostic dilemma: is "Alzheimer's dementia" Alzheimer's disease, vascular dementia, or both? The Lancet Neurology, Volume 3, Issue 3, Page 141, March 2004
9. Ivan Casserly, Eric Topol Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. THE LANCET , Vol 363, 1139-46, April 3, 2004, www.thelancet.com