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THE CORRELATION BETWEEN COGNITIVE DECLINE AND THE INCIDENCE AND THE INFLUENCE OF METABOLIC SYNDROME IN ELDERLY SUBJECTS WITH MILD COGNITIVE DECLINE

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ABSTRACT. Introduction: The leading causes of irreversible cognitive impairment of late life are Alzheimer disease (AD) and vascular cognitive impairment, vascular dementia (VD). Purpose: To evaluate the incidence and the influence of the metabolic syndrome and metabolic syndrome components on a third age population with mild cognitive impairment and no prior history of cognitive decline. **Material and method:** The subjects included in this study were admitted in the ER and the Neurology Clinic of "Vasile Goldis" Western University of Arad during a period of 4 years, beginning with 2004. 198 subjects qualified the inclusion/exclusion criteria set for this study. **Results:** Most of the included subjects were men (56.57%). The average age was 68.3 +/- 4.5 years. The incidence of the MetSy in the study group was 39.39. The most significant cognitive decline is associated to the presence of HTA, leukoaraiosis and age with a mean decrease in MMSE score of -4.556, -4.235 and -3.568. **Conclusions:** Mild cognitive impairment is more frequent and significantly associated to metabolic syndrome and other vascular risk factors.

Keywords: cognitive decline, metabolic syndrome, elderly

INTRODUCTION

The leading causes of irreversible cognitive impairment of late life are Alzheimer disease (AD) and vascular cognitive impairment, vascular dementia (VD). Both pathological entities show an exponential risk with age increase. A new pathological and physiological concept is raised by the term "brain at risk" signifying the presence of several ischemic mechanisms such as subcortical ischemic vascular disease, amyloid angiopathy, cortical infarctions. Brain amyloidosis and cerebral ischemia potentiate and may act in a synergistic manner to finally produce Alzheimer disease, vascular dementia, or both (Gorelick P.B., 2003, Hachinski V., 1995).

PURPOSE

The purpose of this study is to evaluate the incidence and the influence of the metabolic syndrome and metabolic syndrome components on a third age population with mild cognitive impairment and no prior history of cognitive decline.

MILD COGNITIVE IMPAIRMENT

Mild cognitive impairment (MCI) is a general term most commonly defined as a subtle but measurable memory disorder. A person with MCI experiences memory problems greater than normally expected with aging, but does not show other symptoms of dementia, such as impaired judgment or reasoning. The MMSE scores in MCI vary between 28 and 21 points on the scale (Hachinski V., 1995).

Compared with the large body of information about Alzheimer's disease, research about MCI is at a relatively early stage. Because scientists are still answering basic questions about this disorder, it is

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important to note that the definition of MCI is itself a "work in progress." Also, mild cognitive impairment is a transition stage between the cognitive decline of normal aging and the more serious problems caused by Alzheimer's disease. The disorder can affect many areas of thought and action - such as language, attention, reasoning, judgment, reading and writing. However, the most common variety of mild cognitive impairment causes memory problems (Iadecola C. et al., 2003).

In 2001, the American Academy of Neurology (AAN) published practice guidelines for the early detection of memory problems. The AAN workgroup of specialists identified the following criteria for an MCI diagnosis:

- an individual's report of his or her own memory problems, preferably confirmed by another person
- measurable, greater-than-normal memory impairment detected with standard memory assessment tests
- normal general thinking and reasoning skills
- ability to perform normal daily activities (Vagnucci A.H. et al., 2004).

RISK FACTOR FOR VASCULAR DEMENTIA

The risk factors for VD would be the same as those for stroke. Risk factors for vascular dementia may be divided into four major classes:

- demographic,
- atherosclerotic,
- genetic,
- stroke-related.

The demographic risk factors are age, male sex, and lower educational level. The major atherosclerotic risk factors are history of hypertension, cigarette smoking, myocardial infarction, diabetes mellitus, and hyperlipidemia. The genetic factors included such familial vascular encephalopathies as cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL). The stroke-related factors were volume of cerebral tissue loss, evidence of bilateral cerebral infarction, strategic infarction (e.g., thalamic, angular gyrus, or subcortical frontal infarction), and white matter disease. Silent cerebral infarcts, cerebral atrophy, and ventricular size are also believed to play a role in heightening the risk of VD (Hachinski V., 1995, Schneider J.A. et al., 2004).

RISK FACTORS FOR ALZHEIMER DEMENTIA

Worldwide, AD is the most common form of irreversible dementia of late life. The prevalence is around 1.5% at age 65 years and doubles every 4 years to reach about 30% at age 80 years. AD incidence increases with age and is about 1% per year. It may be lower in men and in persons of African and Asian origin.

The early onset of AD is less common, about 6% to 7% of all cases, of which 7% of early-onset are familial cases. These cases generally are determined by an autosomal dominant form of inheritance. Family linkage studies and DNA sequencing point to mutations including the gene encoding β-amyloid precursor protein on chromosome 19, presenilin 1 (PSEN1) on chromosome 14, and presenilin 2 (PSEN2) on chromosome 1. In the case of these 3 gene mutations, AD appears to result from increased production of AB42. These mutations can shift the cleavage site to favor the gamma-secretase site and increased production of the toxic AB42 over the less toxic AB40 peptide (Casserly I. et al., 2004).

Beyond age, risk factors for AD have remained elusive. Lower levels of education have also been associated with AD; however, it has been unclear whether this is attributable to poor compensatory strategies that hasten recognition of the disease or, for example, to adverse exposures earlier in life that might heighten risk of dementia. Other factors such as female sex, infection of various types, lipid concentrations and history of head injury, head circumference, and hormone replacement therapy might be factors that interact with apoE genotype to modify disease

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risk. Thyroid dysfunction and preceding history of depression have also been associated with dementia in observational epidemiological studies (Casserly I. et al., 2004).

A new focus of study in AD has been atherosclerotic vascular risk factors and the corresponding interventions that might reduce risk. Several studies have highlighted the possible role of hypertension, diabetes mellitus, smoking, lipids, hyperinsulinemia, homocysteine, physical inactivity, fat intake and possible protective dietary factors (e.g. fish consumption, vitamins E and C), atrial fibrillation, systemic markers of atherosclerosis, and other vascular factors that may increase or decrease risk of cognitive impairment, AD, or VCI (Chui H., 2000).

The most common genetic and environmental risk factors for AD and atherosclerosis may be summarized as follows:

- apoE e4 polymorphism,
- hypercholesterolemia,
- hypertension,
- hyperhomocysteinemia,
- diabetes mellitus,
- metabolic syndrome,
- smoking,
- systemic inflammation,
- increased fat intake,
- obesity.

There are some cardiovascular drugs with potential therapeutic benefit in AD based on the following mechanisms: cholesterol homeostasis, antiinflammatory properties, antiangiogenic properties. The cardiovascular drugs with possible beneficial effects in AD include:

- angiotensin converting enzyme inhibitors,
- angiotensin II blockers,
- peroxisomal proliferator activating receptor agonists,
- acyl Co-A cholesterol acyl transferase inhibitors,
- statins,
- aspirin,
- nonsteroidal antiinflammatory drugs,
- cyclo-oxygenase 2 (COX-2) inhibitors,
- thienopyridines.

Long-term treatment with some of these interventions in advance of the time of expected cognitive impairment may be important, as the findings from observational epidemiological studies have not been replicated in clinical trials. The observational epidemiological studies suggested that hormone replacement therapy would reduce the risk of cognitive impairment. However, a trial of estrogen plus progestin has shown an increased risk for probable dementia, no prevention of mild cognitive impairment, and a slightly increased risk of meaningful cognitive decline with a mean follow-up time of slightly more than 4 years (Chui H., 2000).

A similar disconnection has been noted for NSAIDS that were touted to reduce the risk of cognitive impairment or decline based on observational epidemiological study results that were not verified in clinical trials. In the case of NSAIDS, the linkage to AD risk is thought to be secondary to polymorphisms in inflammatory mediators such as interleukin 1alfa, interleukin 1beta, interleukin 6, tumor necrosis factor-alfa, alfa-2 macroglobulin, and alfa-1 antichymotrypsin, and the reduction of beta-amyloid protein production (Chui H, 2000). However, postmortem studies have suggested that chronic exposure to antiinflammatory drugs may not alleviate the amount of inflammatory glia, plaques, or tangles. In fact, low-dose steroids may not be useful in the treatment of AD. It has been suggested that NSAIDS might be more effective than steroids, as the former agents have the property of suppression of microglial activation associated with senile plaque formation (Ritchie K, 2002).

Beyond duration of treatment, there are other reasons why HRT and NSAIDS might fail in the setting of randomized controlled trials (Ritchie K, 2002). For example, the target disease state might be too advanced, the agent chosen could have a paradoxical or negative effect (e.g., HRT and COX-2 inhibitors might be prothrombotic), and the patient characteristics of those in clinical trials

might include select subjects who differ from those in the community. These and other explanations could influence the disconnection that we have witnessed between observational studies and controlled trials (Manson J.E. et al., 2003).

RESEARCH DESIGNS AND METHODS

The subjects included in this study were admitted in the ER and the Neurology Clinic of the "Vasile Goldis" Western University of Arad during a period of 4 years, beginning with 2004. Of all the subjects, 198 qualified the inclusion/exclusion criteria set for this study.

The inclusion criteria are:

- Age > 65 years,
- MMSE score < =28 and =>21 points,
- No prior diagnosis of dementia, stroke, silent strokes
- No history of AD,
- No prior history/diagnosis of metabolic syndrome
- Imaging techniques applicable,
- Compliance to study requests.

DIAGNOSIS OF MILD COGNITIVE DECLINE

The subjects were examined using the MMSE test with respect to scores between 21-28 points. The vascular dementia diagnose was based on history of vascular disease, Hachinski score and CT-scan / MRI whenever possible, and the Alzheimer disease exclusion.

Definition of metabolic syndrome

Baseline metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria, which requires the presence of three or more alterations among the following cardiometabolic parameters:

1) elevated systolic (>130 mmHg) or diastolic blood pressure (>85 mmHg) or use of antihypertensive medication,

2) large waist circumference (>88 cm in women and >102 cm in men),

3) high triglycerides (≥150 mg/dl),

4) low HDL cholesterol (men <40 and women <50 mg/dl),

5) elevated fasting glycaemia (≥110 mg/dl) or nonfasting glycaemia (≥200 mg/dl) or antidiabetes medication.

Variables studied:

- Sex
- Age
- Level of education
- Year of retirement where applicable
- MMSE score
- Hachinski score
- SBP (10 mmHg)
- DBP (10 mmHg)
- Waist circumference (cm)
- Triglycerides (mg/dL)
- HDL cholesterol (mg/dL)
- CT/HDL cholesterol ratio
- Fasting glycemia (mg/dL)
- MMSE score (points)
- CTscan / MRimaging results
- Clinical neurological exam

RESULTS

There were included 198 subjects. The demographic distribution according to age groups, sex, educational level, environment, years from retirement is presented in table 1.

Most of the included subjects were men (56.57%) proving that the incidence of probable cardiovascular diseases is higher in male population. The average age was 68.3 ± 4.5 years submitting that MCI and vascular risk factors are more frequent in third age subjects, and that their incidence may increase with age.

Socio-demographical data support the hypothesis that most of the population belong to the rural environment (n=106, 53.54%) and that more than half of the subjects (67.68%) have an educational level lower or equal to high school studies. This particularity may be explained by the social conditions met in the 1940's-1950's Romania where most of the persons were encouraged to graduate at least secondary school, but afterwards were counseled to follow a professional educational training, rather than attending graduate studies.

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Table 1

The social-demographic parameters for the studied subjects

	Sex		Age groups				
	M	**F**	**65-70**	**70-75**	**75-80**	**80-85**	**85>**
n	112	86	57	68	34	25	14
%	56.57	43.43	28.79	34.34	17.17	12.63	7.07

	Level of education						
	None	**Ellementary school**	**Secondary school**	**High School**	**Pre graduate**	**Graduate**	**Post graduate**
n	15	17	38	64	28	27	9
%	7.58	8.59	19.19	32.32	14.14	13.64	4.55

	Urban	**Rural**
n	92	106
%	46.46	53.54

	Years from retirement				
	0 -- 1	**2 -- 3**	**3 -- 4**	**>5**	**working**
n	32	79	51	29	7
%	16.16	39.9	25.76	14.65	3.54

Table 2

The frequency of the metabolic syndrome in the studied group

MetSy	**Yes**	**No**
n	78	120
%	39.39	60.61

Table 3

The components of metabolic syndrome and their frequency in the studied population

Metabolic syndrome diagnostic criteria / components				
	n	**%**	**n**	**%**
HTA	131	66.16	67	33.84
Waist (>102 in men;>88 in women)	145	73.23	53	26.77
Triglycerides≥150 mg/dl	78	39.39	120	60.61
HDL cholesterol (men <40;women <50 mg/dl),	105	53.03	93	46.97
Hyperglycemia	87	43.94	111	56.06

The MMSE scores and their distribution is heterogeneous in the studied group. The minimum score, was as expected and set by the inclusion criteria, 21, and the highest 28. The mean MMSE score was 23.2 +/-2.1 points on the scale. For the metabolic syndrome group the MMSE mean score is lower with -2.345 points compared to non-metabolic syndrome subjects. The data is presented in table 4.

The incidence of the MetSy in the study group was 39.39%. When the whole study population was dichotomized upon MetSy components it was noticed that the highest incidence was for large wais circumference (73.23% of the subjects), followed by hypertension (66.16%) and low HDL cholesterol (53.03%). All these factors, independent, or in conjunction with other risk factors are strong determinants for atherosclerotic risk, stroke and cognitive impairment. A more detailed data analysis is presented in tables 2 and 3.

Table 4

The high, low, and mean MMSE scores for the whole study group, the MetSy subjects and non-MetSy individuals

MMSE score	High	Low	Mean
All	28	21	23.2
MetSy	27	21	21.5
non-MetSy	28	23	25.2

Table 5

The distribution of the subjects according to cerebral CT-scan and MRI results

	CT scan					MRI			
	Lacunes	Leukoaraiosis	Both	Normal		Lacunes	Leukoaraiosis	Both	Normal
n=186					**n=12**				
All	89	45	35	17	**All**	4	3	2	3
MetSy	75	28	18	5	**MetSy**	3	2	1	1
non-MetSy	14	17	17	12	**non-MetSy**	1	1	1	2

Cerebral imaging was performed in all the subjects included, most of them being examined by CT-scan, only 12 subjects underwent cerebral MRI. The results are presented in table 5.

The statistical analysis revealed a statistically significant correlation between modified CT/MRI results and the presence of metabolic syndrome ($p<0.001$) proving that the metabolic syndrome is a recognizable risk factor in cerebrovascular ill subjects, even if here all the findings resumed to silent strokes such as cerebral lacunes and leukoaraiosis.

For a differentiation of possible AD in the subjects studied it was applied the Hachinski ischemic scale which is an attempt to differentiate Alzheimer's type dementia and multi-infarct dementia. Patients are scored according to certain clinical features such as:

- Abrupt onset of dementia 2 points,
- Stepwise deterioration 1 point,
- Somatic complaints 1 point,
- Emotional incontinence 1 point,
- Hypertension (past or present) 1 point,
- History of stroke 2 points,
- Focal neurological symptoms 2 points,
- Focal neurological signs 2 points.

The interpretation of the scale requires a score greater than 2 for typical multi-infarct dementia. A score of 2 or less are typical of a patient with Alzheimer's disease.

When applied to the subjects included in this study, all the scores were above 2, which certified, at least in part, the ischemic mechanism of dementia.

The statistical processing of the gathered data looking for correlations among the variables studied found some significant correlations between cognitive decline and the metabolic syndrome, or its components. The results are presented in table 6 where the MMSE scores were correlated to different variables.

DISCUSSIONS

Aging is characterized by marked inter-individual differences in the rate of cognitive decline. This diversity in patterns of mental decline indicates that, in addition to the effects of normal ageing, other age-associated processes may be at work. In particular, both atherosclerotic cardiovascular diseases and cognitive dysfunction increase in frequency with age in the general population, and growing evidence suggests that cardiovascular diseases may be a modifiable risk factor for cognitive decline in the elderly. It is also increasingly recognized that cardiovascular diseases and cognitive pathology share risk factors, including hypertension, diabetes, and dyslipidemia.

In the present study, the most significant cognitive decline is associated to the presence of HTA, followed by leukoaraiosis and age with a mean decrease in MMSE score of -4.556, -4.235 and respectively -3.568. The HTA may cause cognitive decline by lipohyalinosis in the small penetrating brain arteries determining leukoaraiosis, or cerebral lacunes.

Dyslipidemia and hyperglycemia are associated to a more severe cognitive decline may be due to vascular wall alterations in atherosclerotic arteries. Atherosclerosis is an important cause for silent strokes and thus it may contribute to the formation of strategic strokes that determine cognitive impairment.

Table 6

The statistical significance of the correlations between different variables and cognitive decline

	p	Mean difference	Confidence interval
HTA	<0.001	-4.556	95%
Leukoaraiosis	<0.001	-4.235	95%
Age	<0.001	-3.568	95%
HDL cholesterol (men <40;women <50 mg/dl)	<0.001	-2.564	95%
Waist (>102 in men;>88 in women)	=0.045	-2.351	95%
MetSy	=0.001	-2.345	95%
Hyperglycemia	=0.065	-1.897	95%
Triglycerides≥150 mg/dl	=0.023	-1.651	95%
Lacunes	=0.189	-0.265	95%
Education	=0.065	1.562	95%

Large waist circumference is associated to intra-abdominal obesity and insulin resistance. In this manner it may be involved in vascular degeneration with atherosclerotic changes and cognitive decline by multi-infarct mechanisms.

Leukoaraiosis and cerebral lacunas know as silent strokes, are correlated to cognitive decline due to their alteration of neuronal circuits, especially in the whit periventricular matter where some of the memory circuits are lying.

The higher the level of education, the higher the MMSE score. Thus, education acts as a protector against cognitive decline in the studied population, and it correlates to early retirement, meaning that the shortest the period of time from retirement, the better MMSE scores are.

The metabolic syndrome correlates to lower MMSE scores, and thus mild cognitive decline. It is quite easily understood that a condition where dyslipidemia, insulin resistance, HTA, and hyperglycemia is related to diffuse ischemic alterations of the cerebral matter. In this study this was certified by using CT-scan and cerebral MRI techniques that revealed lacunes, leukoaraiosis, or both in 89.89% of the subjects.

The Hachinski scores related the cognitive decline to multi-infarct dementia, but it may not be clearly stated that all the subjects included here did not present with Alzheimer disease. Supplementary diagnosis criteria should have been added in order to exclude those subjects (Hachinski V., 1995). However, recent studies state clear that Alzheimer disease share some common vascular risk factor with vascular dementia, the two sometimes coexisting, and thus a clear separation line between the two nosologic entities is difficult to draw (Etminan M. et al., 2003).

Vascular risk factors are typically thought to produce deleterious effects on brain function via overt strokes. However, it is more likely that the burden of brain lesions due to cerebrovascular disease actually

accumulates subclinical over years or decades. Cross-sectional data in elderly demented individuals have shown that various cardiovascular risk factors are associated with a higher risk of dementia. Studies have also shown clear relationships between diabetes mellitus, cognitive decline, and dementia (usually vascular dementia). The term "vascular cognitive impairment" was proposed to describe mild-to-severe cognitive impairment of a primarily vascular basis. Few have investigated comprehensively neuro-psychological functioning in cognitively intact individuals with vascular diseases. Specifically, longitudinal data on the pattern of cognitive decline in elderly people with different clinical types of cardiovascular disease are lacking (Elias M.F. et al., 2004). At present, however, it is not clear whether stroke is associated with a progressive decline in either global or specific cognitive abilities, and whether such a relationship exists independently of concomitant vascular risk factors.

CONCLUSIONS

Mild cognitive impairment is more frequent and significantly associated to metabolic syndrome and other vascular risk factors. Vascular deterioration in concordance to cognitive decline presents a strong relationship when the subjects associate metabolic syndrome. Hypertension, leukoaraiosis and age are the three most remarkable negative influencing factors for cognitive decline. Educational level appears to act as a protector for cognitive deterioration, but it shall not counteract the negative effect of dyslipidemia, or intra-abdominal adiposity (large waist circumference), nor the catastrophic effect of hyperglycemia.

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