Importance of CAIDE risk score for the early diagnosis of Alzheimer dementia

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ABSTRACT

Alzheimer's disease is the most common type of dementia and accounts for about 60%–80% of diagnosed dementias. Currently, there are 5.3 million people in the United States diagnosed with AD, and this number is expected to increase markedly by 2050. In Romania the number of diagnosticated cases went up to 4.4 million in 2011, which represents 20.5% of the total population.

Alzheimer's disease (AD) is a critical public health problem with a significant social and financial burden on society. Paradoxically, the more the disease is detected later, the higher the overall cost of care, without taking into account the quality of life of the patient and the family, the actual human suffering caused by the disease. The most important thing is that there is no single test for Alzheimer's disease, so early identification of risk factors for Alzheimer's dementia is very important because the neurodegenerative processes of the disease can begin in the middle of life. Identifying these risk factors can shed light on the pathophysiology of Alzheimer's disease, thus providing new potential ways to prevent and treat it.

KEYWORDS:

Dementia, CAIDE score, Alzheimer, diagnostic

INTRODUCTION-IMPORTANCE OF THE PROBLEM

Alzheimer disease (AD) is a critical public health problem with an enormous social and financial burden on society. AD is a chronic disease, a progressive neurodegenerative disorder with long preclinical and prodromal stages (20 years) and average clinical duration of 8-10 years. The disease has an estimated prevalence of 10-30% in the population > 65 years, and an incidence of 1-3%. Most AD patients (> 95%) have the sporadic form of disease, which is characterized by a late onset (80-90 years), and annually, in USA alone, about \$ 200 billion is spent on direct care of patients with dementia. (1,2)

In elderly patients dementia is most often an overlap between AD and vascular dementia, especially when the onset in the old-old who associate cardiovascular risk factors. Necroptic examination often shows signs of AD, vascular and Lewy body dementia together. (3)

In view of supporting the above mentioned data, N.K. Seetlani et al. published in September 2016 the results of a transversal descriptive study concluding that the incidence of AD and vascular dementia is quite high in the population, and early detection and prompt treatment can reduce the burden of the disease in the general population.(4)

The early diagnostic efforts were focused on patients in the dementia stage of AD, but recently the importance of a pre-dementia stage preceding the clinical onset of AD was recognized. Therefore, many studies are now being focused on individuals with normal cognitive status and modifiable cardiovascular risk factors, considered to be the best strategy to increase the prevalence and reduce the incidence of AD. (5)

The aim of this study was to present a simple method available to all physicians for identifying people at risk for AD based on the Cardiovascular Risk Factors, Aging and Dementia (CAIDE risk score).

Early identification of the risk factors for Alzheimer dementia is very important because the neurodegenerative processes of this disease can occur during midlife. Their identification can shed light on the

pathophysiology of AD, thus providing new potential modalities for its prevention and treatment.

CAIDE RISK SCORE

In 2006, the first risk score for the prediction of dementia in 20 years among middle-aged people was developed. Its purpose was to investigate the association between social status, lifestyle, cardiovascular risk factors and cognition and risk of dementia and structural brain changes. Professor M. Kivipelto is leading the CAIDE project aimed at identifying the individuals at high risk of dementia, in which preventive intensive treatment may improve the disease course, and developing a simple method for predicting the risk of dementia in middle-aged individuals based on the individual risk profile.(6)

The researchers had implemented this tool in a random sample of 2,000 middle-aged people, concurrently participating in 2 Finnish studies:

- The Northern Karelia Study – The extremely high cardiovascular mortality had caused great concern among the local population. The action to reduce the problem was demanded in a petition addressed to the Finnish government signed by local community representatives. In response, the North Karelia project was launched in 1972 being aimed at developing a comprehensive community prevention program. After the first five years, prevention activities had also been initiated nationwide. The main goal was to reduce serum cholesterol, blood pressure and smoking, with lifestyle changes and improved drug treatment, especially for high blood pressure. Major decreases were recorded in serum cholesterol, blood pressure, and number of smokers. Coronary mortality decreased by 84% in the middle-aged population between 1972 and 2014. Approximately two-thirds of the decrease in mortality rate was accounted for by changes in risk factors and 1/3 by improved new treatments developed since the 1980s.(7, 8, 9)

- The Framingham study was a reference study which ever since the 1960s has provided strong evidence of the possibly causal role of several lifestyle factors in the development of cardiovascular diseases (CVD). At that time, the Finnish men had the highest coronary heart disease mortality rate in the world, finding that generated great local concern. In 1972, a pioneering project by a young leadership team and with many partners, the World Health Organization included, began to change the situation. The project was based on the results of the Framingham and other classical studies with the goal to develop a comprehensive prevention program to reduce the levels of risk factors in the population through general lifestyle changes in the Northern

Karelia pilot area. Subsequently, the program was extended nationwide. Over the years, significant reductions in the levels of risk factor among the population associated with a dramatic decline in age-adjusted CVD mortality rates and public health improvement were recorded.(10)

Thus, M. Kivipelto et al. had focused on cardiovascular diseases and re-examined the same patients after 20 years for signs of dementia. Several midlife cardiovascular risk factors were studied to create the scoring tool, the scores being estimated based on β coefficients and dementia risk score was the sum of these individual scores (range 0-15) quantified as follows in Fig 1.

RISK FACTOR		POINTS	TOTAL SCORE	DEMENTIA RISK
AGE	<47 years	0	0-5	1 %
	47-53 years	3		
	>53 years	4		
EDUCATION	≥10 years	0	6-7	1,9 %
	7-9 years	2		
	≤6 years	3		
GENDER	F	0	8-9	4,2 %
	M	1		
BLOOD PRESSURE	≤140mmHg	0	10-11	7,4 %
	>140mmHg	2		
BODY MASS INDEX (kg/m ²)	≤30	0	12-15	16,4 %
	>30	2		
HYPERCHOLESTEROLEMIA	YES	0		
	<251,35mg/dl			
	NO	2		
PHYSICAL ACTIVITY	>251,35mg/dl			
	YES	0		
	NO	1		

Fig 1. The CAIDE risk score and interpretation.

This multidisciplinary study has provided over the past few years sufficient evidence that cardiovascular risk factors (hypertension, obesity, hypercholesterolemia, smoking, cardiovascular disease) and psychosocial factors contribute significantly to the cognitive decline (dementia and AD) and that a healthy diet can reduce the risk of disease. (11)

In 2006, T. Ngandu published a project focused on demonstrating the important role of lifestyle in the development of dementia and cognitive disorders. Particular attention was paid to possible interactions between lifestyle and genetic risk factors. The overall hypothesis was that a healthy lifestyle could reduce the risk of dementia and occurrence of cognitive impairment. Briefly, this set of studies has shown that risk factors associated

with unhealthy midlife lifestyle, such as obesity, hypertension and hypercholesterolemia increase the risk of dementia and AD later in life. (12)

Cardiovascular risk factors among adults have been consistently associated with structural brain aging, such brain diseases as white matter atrophy and abnormalities, as well as the decline in cognitive processing speed and executive function.

Epidemiological evidence suggests an association between AD and vascular risk factors, and their control could prevent the development of dementia. (13)

○ Age

The most common risk factor for AD is aging, but AD is not a "normality" of aging; age increases the risk, but is not a direct cause of AD. Most people with AD are over 65 or older. After the age of 65, the risk of developing AD doubles every five years; after the age of 85, the risk reaches almost one-third. (13)

○ Education level

In 2011, E.S. Sharp et al. reported, in order to reinforce Katzman and Mortimer's conclusion, that a low education level is a risk factor for developing dementia. They suggested that the relationship between education and dementia may be more complex than previously described in literature. The results of the published study suggest that a low education level is associated with an increased risk of dementia. Moreover, the education level most commonly associated with the highest risk of dementia varies considerably depending on the region, as well as age, sex, race or ethnicity. (14, 15, 16)

○ Physical activity

Moderate exercise should be considered as a standard recommendation for reducing cognitive decline, as a result of the improvement in neurodegenerative mechanisms and increase in neuroplastic and neuroprotective neurotrophic factors. Therefore, it is suggested that exercise is an important neuroprotective modulator that brings significant control of the disease and amplifies brain functions. (17, 18, 19)

○ Arterial blood pressure

It is a common and potentially modifiable risk factor not only for cardiovascular and cerebrovascular diseases but also for AD. Studies have shown that elevated blood pressure (BP), especially in midlife, is associated with higher AD risk later in life. Y.H. Shih et al. published the results of an original study in which they aimed at testing the possible relationship between hypertension (HTN) and late AD onset. He used two animal models (1) genetically modified pigs and (2) mice expressing three AD-related mutant genes in order to examine the role of HTN in the pathogenesis of AD. In the group of young animals, HTN has been shown to accelerate AD-associated pathologies, induces microglia activation and shrinkage of hippocampal dendritic complexity, and impairs hippocampus-dependent learning and memory. These findings suggest that HTN accelerates AD onset. BP control, especially in midlife, is an important way of delaying the onset of AD. (20, 21, 22, 23)

○ Cholesterol

The associations between cholesterol, stroke, cognitive impairment and dementia are complex and not fully understood, yet. Given the population aging, it is imperative to develop strategies for the prevention and treatment of dementia. High total serum cholesterol (C) levels in middle-aged patients increase the risk of late-life AD, and was also linked to specific AD changes occurring at brain level. Recent data suggest a bidirectional relationship between C and dementia; high C levels represent a risk factor for the development of AD in 20 years. (24) Solomon et al. believe that doctors tend to confine AD and VD to geriatric age borders and address symptoms as they occur. The conclusion of their study highlights the importance of addressing risk factors during midlife before the disease or symptoms occur. High serum cholesterol during midlife increases the risk of both AD and VD. Moreover, dementia and cardiovascular disease represent major health problems, share many risk factors and often occur simultaneously, interacting with each other. Efficient management of these disorders

justifies a cross-disciplinary approach. (24)

The CAIDE study later laid the foundation for the Finnish FINGER study to prevent cognitive impairment and disability. The Finnish Geriatric Intervention Study for the Prevention of Cognitive Disorders and Disability, a randomized controlled trial, aimed to assess a multidimensional approach for preventing cognitive decline in the elderly at high risk in the general population. Between September 7, 2009 and November 24, 2011, 2654 persons were enrolled and randomly assigned to the intervention or control group (25)

The results of this controlled study showed that multidimensional intervention could improve or preserve cognitive function and reduce the risk of developing new chronic diseases in the elderly at high risk in the general population. (26)

Currently, there is no effective treatment for dementia, and population screening is not supported as in the absence of disease-modifying treatments there is no evidence that the benefit of screening exceeds potential risk. However, in the conversion of dementia, as a result of previous stages of cognitive decline, focusing on "modifying" cardiovascular risk factors has a great potential and to prevent or delay cognitive decline. (27)

The CAIDE dementia risk score was initially a new approach for predicting the risk of Alzheimer dementia, but it should be validated for Romania and further improved to increase its predictive value. This approach highlights the role of cardiovascular factors in the development of dementia and could help identify people who might benefit from intensive lifestyle and pharmacological interventions.

To this date, CAIDE data have resulted in nine dissertations and over thirty original scientific papers published in high impact journals. It is essential to further assess predictability in larger, less homogeneous populations and to determine whether it can be improved by taking into account other midlife risk factors.

Taking into account the presented data and the absence of data in the Romanian population, we aim to carry out a prospective study of the CAIDE score in the midlife general population. Thus, we started enrolling patients aged 40-65 years who will be divided into two groups: with or without cardiovascular risk factors, each group consisting of about 50 participants. They will be followed-up annually with respect to the cardiovascular risk factors, cognitive and nutritional status.

CONCLUSIONS

There is overwhelming and converging evidence in the literature showing that cardiovascular risk factors play a very important role in the etiology of AD. Even though for some of these factors the mechanisms that associate them with AD are very clear, for others the association with AD is much more complex and therefore further research is needed. Taking into account that these cardiovascular factors are currently the only ones known as modifying risk factors for AD, the possibility of intervening on them in order to prevent or delay the onset of AD deserves more dedicated research and rigorous prevention.

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