THE COGNITIVE DISORDER IN THE CONTEXT OF METABOLIC SYNDROME

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Abstract: *The relation between the mild cognitive disorder and the metabolic syndrome is strongly debated in the literature in recent times, but until now, the data are still incomplete to draw a coherent conclusion. Both conditions represent real public health issues: the first represents a morbid transition state from the physiological aging to Alzheimer's disease, and the metabolic syndrome is proven to be the cause of cardiovascular and cerebrovascular pathology. This review aims at analysing the data from literature regarding the relation between the metabolic syndrome and cognitive disorders.*

Cuvinte cheie: *sindrom metabolic, tulburare cognitivă*

Rezumat: *Relația dintre tulburarea cognitivă ușoară și sindromul metabolic este puternic dezbătută în literatura de specialitate din ultima vreme, însă până în momentul de față, datele sunt incomplete pentru a trage o concluzie adecvată. Amândouă condițiile reprezintă probleme reale de sănătate publică: tulburarea cognitivă ușoară, ca stare morbidă de tranziție de la îmbătrânirea fiziologică la boala Alzheimer, sindromul metabolic prin legătura cu patologia cardiovasculară și cerebrovasculară. Prezenta recenzie își propune să analizeze datele din literatura de specialitate privind conexiunea dintre sindromul metabolic și tulburarea cognitivă.*

The metabolic syndrome represents a cluster of risk factors which significantly increase the incidence of simultaneously occurring diseases, such as type 2 diabetes, coronary heart disease, and ischemic strokes.(1) Metabolic syndrome is present when three or more of the following are found:(2)

1. blood pressure > 135/85 mmHg;
2. fasting blood sugar > 110 mg/dL;
3. abdominal circumference - male > 102 cm; female > 88 cm;
4. low HDL – cholesterol - male below 40 mg/dL; female below 50 mg/dL;
5. serum triglycerides over 150 mg/dL.

Along with these diagnostic criteria proposed by the U.S. National Programme on Cholesterol Education, the World Health Organization proposes the introduction of insulin resistance.

Mild cognitive impairment (MCI) is a morbid condition, a transition from the physiological aging to Alzheimer's disease. In terms of presentation, it is divided in the amnestic form, with impaired memory (mainly associated with Alzheimer's disease) and non-amnestic, with other cognitive functions except the memory impairment, in the context of vascular dementia, Lewy body dementia and fronto-temporal dementia.

The study of Vikarunnessa, recently published in the Journal of Alzheimer's Disease (3), based upon the results of the study CAIDE (4) conducted at the Karolinska Institute in Sweden, brings into question the role of LDL – cholesterol phenotype in relationship with MCI. The authors found a link between small molecular size LDL phenotype that occurs as a result of the inadequate metabolism of VLDL cholesterol changing the plasma levels of triglycerides and HDL – cholesterol, common finding in metabolic syndrome. Patients with MCI and Alzheimer's disease have shown constant hypertriglyceridemia, low HDL – cholesterol and small dimensions LDL phenotype in comparison with patients from the control group, statistically significant. Currently, there is a consensus regarding the aberrant inflammatory response that occurs in the metabolic syndrome, but the connection with MCI and Alzheimer's disease remains at the level of speculation.(5) Until now, the pathogenesis of Alzheimer's disease is linked to neurodegeneration and β-amyloid accumulation. Amyloid plaques are polymer aggregates, but they seem not to be aggressive agent, but the amyloid olygomers that alter the synaptic structure through specific membrane site binding. Alteration of the tau protein, a stabilizer protein of axonal microtubules, constitutes a complementary path in this pathogenesis. Excessive hyperphosphorilation of tau protein triggers microtubular dezintegration, axonal degeneration and formation of insoluble neurofibrillary tangles in the somatodendritic endings.(6)

Tau is firstly found in the entorhinal area, then in all the hippocampal formation and later in the whole neocortex. Unlike tau protein, β-amyloid can be found primary in the frontal cortex.(6)

Apolipoprotein E is an intermediate density lipoprotein necessary to the catabolism of other rich triglycerides lipoprotein. It is produced in the central nervous system by astrocytes and seems to be associated with Alzheimer's disease, ischemic heart disease, atherosclerosis and diabetes. The ε4 allele presence is considered a risk factor for non – familial forms of Alzheimer's disease, no relationship is

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known exactly, but an inefficiency of the effect of the degradation of amyloid is presumed.(7)

A Korean study has shown that the isoforms of apoE4 have been correlated with high plasma levels of LDL – cholesterol, but unchecked statistically probably due to the small number of patients studied.(8) Recently, it was found out about the role of apoE4 variant, which limits the HDL – cholesterol binding, but also binds the VLDL preferentially inhibiting the normal lipid clearance with the global increase of the total serum cholesterol level.(9) The link between the lipid metabolism and the cognitive disorder is not just limited at the alleged relationship between apoE, accumulation of β-amyloid and tau protein and insoluble aggregates.(10) As we mentioned above, the new diagnostic criteria of metabolic syndrome include insulin resistance. This is a metabolic disorder induced by the inadequate consumption of food and it is defined as a decrease in insulin response, high serum glucose and low cellular use. At the level of the central nervous system, the insulin can cross the blood–brain barrier, with different effects depending on the specific receptor signalling. Insulin receptors are found in greater numbers in the brain areas with increased glucose metabolism, such as the hippocampal formation.(11) An interesting study (12) published in 2012 indicates that insulin resistance in patients with metabolic syndrome is correlated with insulin signalling disorders at cerebral level. Fructose and the deficit of docosahexaenoic acid (omega-3 class) increase insulin resistance of hippocampal neurons by altering the phosphorilation of the insulin receptor. Synaptophysine, a synaptic marker (13), is severely decreased in the same manner described above, impairing the synaptic neuroplasticity. Docosahexaenoic acid deficiency is associated with a spatial memory disorders in the Barnes maze test.(12) The study has major limitations, mostly the fact that it was conducted on laboratory animals, requiring a confirmation on a study with human subjects.

Actual research has correlated the metabolic syndrome with MCI and Alzheimer's disease, without finding a direct causal relationship. Non-amnestic MCI and its switch into the vascular dementia, most often have to do with metabolic syndrome by the diffuse cerebral atherosclerosis, small arterial lesions (lipohialinosis) from the lacunar state, stroke and hemorrhage lesions. In the current day neurology, the cerebrovascular disease is often associated with metabolic syndrome but also with cortical dementia of Alzheimer's type, letting us to speak about a diagnosis of Alzheimer's disease with vascular complications, the outdated mixed dementia. However, we frequently see the metabolic syndrome in patients with MCI or Alzheimer's disease with early onset, where the vascular component did not have the time to manifest.

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