Link between metabolic disorders and Alzheimer's disease examined

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No effective treatments are currently available for the prevention or cure of Alzheimer's disease (AD), the most frequent form of dementia in the elderly. The most recognized risk factors, advancing age and having the apolipoprotein E Ɛ4 gene, cannot be modified or treated. Increasingly, scientists are looking toward other risk factors to identify preventive and therapeutic strategies. Much attention recently has focused on the metabolic syndrome (MetS), with a strong and growing body of research suggesting that metabolic disorders and obesity may play a role in the development of dementia.

A new supplement to the *Journal of Alzheimer's Disease* provides a state-of-the-art assessment of research into the link between metabolic syndrome and cognitive disorders. The supplement is guest edited by Vincenza Frisardi, of the Department of Neurological and Psychiatric Sciences, University of Bari, and the Geriatric Unit and Gerontology-Geriatrics Research Laboratory, IRCCS, Foggia, Italy, and Bruno P. Imbimbo, Research and Development Department, Chiesi Farmaceutici, Parma, Italy.

The prevalence of MetS and obesity has increased over the past several decades. MetS is a cluster of vascular and metabolic risk factors including obesity, hypertension, an abnormal cholesterol profile, and impaired blood glucose regulation. "Although molecular mechanisms underlying the relationship between MetS and neurological disorders are not fully understood, it is becoming increasingly clear that cellular and biochemical alterations observed in MetS may represent a pathological

bridge between MetS and various neurological disorders," explains Dr. Frisardi.

Type 2 diabetes (T2D) has been linked with cognitive impairment in a number of studies. The risk for developing both T2D and AD increases proportionately with age, and evidence shows that individuals with T2D have a nearly twofold higher risk of AD than nondiabetic individuals.

Paula I. Moreira, Faculty of Medicine and Center for Neuroscience and Cell Biology, University of Coimbra, Portugal, outlines some of the likely mechanisms. Both AD and T2D present similar abnormalities in the mitochondria, which play a pivotal role in cellular processes that impair their ability to regulate oxidation in the cell. Human amylin, a peptide that forms deposits in the pancreatic cells of T2D patients, shares several properties with amyloid-ß plaques in the Alzheimer's brain. Insulin resistance is another feature shared by both disorders. Impairment of insulin signalling is directly involved in the development of tau tangles and amyloid ß (Aß) plaques. "Understanding the key mechanisms underlying this deleterious interaction may provide opportunities for the design of effective therapeutic strategies," Dr. Moreira notes.

In another article, author, José A. Luchsinger of the Division of General Medicine, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, notes that while there seems to be little dispute that T2D can cause cerebrovascular disease and vascular cognitive impairment, whether T2D can cause late onset AD remains to be determined. "Although the idea is highly speculative, the association between T2D and cognitive impairment may not be causal. Several lines of evidence provide some support to the idea that late onset Alzheimer's disease could cause T2D, or that both could share causal pathways," he notes. He reviews epidemiological, imaging, and pathological studies and clinical trials to provide insight. "Given the epidemic of T2D in the

world, it's important to determine whether the association between T2D and cognitive impairment, particularly late onset AD, is causal and if so, what are the mechanisms underlying it."

Dr. Frisardi notes that most efforts by the pharmaceutical industry have been directed against the production and accumulation of amyloid-ß. "Unfortunately, these efforts have not produced effective therapies yet, since the exact mechanisms of AD are largely unknown. Given that the onset of AD most likely results from the interaction of genetic and environmental factors, the research agenda should consider new platforms of study, going beyond the monolithic outlook of AD, by synthesizing epidemiological, experimental, and biological data under a unique pathophysiological model as a point of reference for further advances in the field."

More information: Metabolic-Cognitive Syndrome: Update on the Metabolic Pathway in Neurodegenerative Disorders, Guest Editors: Vincenza Frisardi and Bruno P. Imbimbo
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