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EDITORIAL

Diabetes mellitus and Alzheimer's disease: An unforgettable relation☆

Diabetes mellitus tipo 2 y enfermedad de Alzheimer: una relación para no olvidar

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Type 2 diabetes mellitus (T2DM) is a disease that currently affects 180 million people worldwide. Furthermore, it is expected that there will be more than 300 million patients with T2DM by 2025 as the result of demographic growth, aging, obesity, and sedentary lifestyles. In recent years, patients with T2DM have been shown to be at greater risk of developing dementia, both as vascular dementia and Alzheimer's disease (AD).[1] AD is the most common cause of dementia and is characterized by a progressive amnesic disorder with the subsequent occurrence of other cognitive, behavioral, and neuropsychiatric changes that prevent general social functioning and the performance of the regular activities of daily life.

In fact, as compared to subjects without diabetes, patients with T2DM can suffer from several degrees of cognitive impairment from the very early stages of the disease. A scale of cognitive impairment associated with T2DM prior to dementia has been proposed: a) cognitive dysfunction associated with diabetes, during which patients have subjective complaints of memory, with a subtle change in neuropsychological tests (usually 0.3–0.5 SD less than subjects with no diabetes); b) mild cognitive impairment (MCI), in which patients have a score of minus 1–1.5 SD.[2] People with MCI have memory problems, but are able to perform everyday activities. It should be noted that the annual rate of conversion to dementia in patients with MCI ranges from 10% to 30%, and that the risk factors that accelerate the progression of cognitive impairment are as yet unknown. In recent years, research on MCI has focused on the identification of the factors that promote conversion to dementia, especially AD. Thus, several neuropsychological tests, cerebrospinal fluid biomarkers, and neuroimaging tests have been evaluated as predictors to assess the risk of conversion to dementia. However, the methods proposed have no adequate predictive value and are not sufficiently standardized for their use to be recommended in clinical practice. The detection of the apolipoprotein E genotype (APOE ε4)—associated with a high risk of AD—in order to assess the risk of conversion to dementia is not recommended either. Biessels et al. proposed a score of the 10-year risk of progression to dementia in patients with T2DM based on age, the presence of chronic complications of diabetes, depression, and educational level.[2]

It should be noted that the relationship between T2DM and AD is independent of vascular involvement.[3] Thus, the increased incidence of AD seen in the population with T2DM could be attributed to neurodegeneration caused or accelerated by diabetes itself.

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An argument supporting neurodegeneration accelerated by diabetes is the pathophysiology of diabetic retinopathy, traditionally described as a microvascular complication. There is, however, ample evidence to suggest that retinal neurodegeneration is an early event in the pathogenesis of diabetic retinopathy and that it is involved in microvascular changes.[4] The retina and the brain have the same embryological origin and share many anatomical and functional characteristics (such as the microvascular bed and the blood–tissue barrier system). Indeed, approximately 40%–50% of patients with AD have some type of abnormality in electrophysiological studies of the retina.[5] Moreover, in patients with AD, and even in those with MCI, a decreased thickness of the retinal ganglion cell layer (the retinal layer showing the earliest and greatest involvement in diabetes) has been seen.[6]

T2DM induces both functional and structural changes in the brain. Interestingly, several studies of patients with T2DM have demonstrated a loss of brain volume similar to or up to three times greater than the atrophy rate due to natural aging.[7] In addition, smaller brain volumes in patients with T2DM have been associated with greater insulin resistance and longer diabetes duration. However, controversy still exists as to whether brain atrophy contributes specifically to memory deficits in patients with T2DM. Magnetic resonance imaging with diffusion tensor imaging (MRI-DTI) allows white matter function to be evaluated. Using this technology, patients with T2DM have been shown to have microstructural abnormalities in white matter tracts that condition defects in information processing.[8] It should be noted that such abnormalities in white matter may already be seen in patients with T2DM, and even in patients with metabolic syndrome, with no cognitive impairment. Such patients have a poorer score in neuropsychological assessment tests. The presence of T2DM has also been shown to alter glucose uptake by neurons, as assessed by SPECT of the brain.[9]

The relation between T2DM and AD is even more interesting bearing in mind that the metabolic pathways triggered by hyperglycemia and insulin resistance (decreased insulin signaling, inflammation, oxidative stress, advanced glycation end products) are precisely those involved in the pathogenesis of AD. Insulin is essential for neuron survival,[10] and a decreased number of insulin receptors have been seen in the brains of patients with AD.[11] Defective insulin signaling in the brain may play an essential role in the conversion to dementia in patients with T2DM. It has also been reported that the administration of intranasal insulin (which has no systemic effects) is associated with a significant improvement in cognitive performance in healthy adults[12] and patients with early AD.[13] In fact, clinical trials are ongoing to assess the value of intranasal insulin to prevent the conversion of MCI to AD. On the other hand, neurons are known to have a receptor for GLP-1. GLP-1 bound to its receptor triggers the same signaling pathways as insulin itself, critical pathways for neuron survival, conferring a neuroprotective effect[14]. Clinical trials are ongoing to assess the effect of GLP-1 analogs on the conversion to AD in patients with MCI.

Finally, T2DM and AD each have a significant genetic load. A systematic search carried out by our group through the AlzGene and PubMed databases identified the following 10 genes common to T2DM and AD: APP (amyloid β A4 precursor protein), APOE (apolipoprotein E), AMPK (protein kinase, AMP-activated, γ2 subunit), FTO (fat mass and obesity), PPAR-γ (peroxisome proliferator activated receptorγ), SORCS1 (sortilin-related VPS10 domain containing receptor 1), IDE (insulin-degrading enzyme), ABCA1 (ATP-binding cassette sub-family A member 1), VEGF (vascular endothelial growth factor), and PCK1. Most these genes encode proteins involved in both the development of T2DM or its complications and in AD, but their role in the relationship between the two diseases has yet to be elucidated.

Finally, T2DM and AD are both age-related and highly prevalent diseases. An established relation exists between them, with T2DM acting as an accelerator of the progression to AD. New approaches that will allow us to identify those diabetic patients at the greatest risk of experiencing AD are needed. This would make possible the early implementation of potential therapeutic strategies that prevent or slow the development of this devastating disease.

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