Commentary

Insulin Resistance, Obesity, and the Risk of Neurodegenerative Diseases

Bruno Vellas¹ and Alan Sinclair²

¹Alzheimer’s Center, Department of Geriatrics Medicine, Toulouse Hospital University, France.
²Diabetes Research Unit, Section of Geriatric Medicine and Gerontology, University of Warwick, Coventry, United Kingdom.

The relationship between body mass index (BMI) and dementia risk was investigated recently in an 18-year follow-up study of a representative cohort of 392 nondemented Swedish adults aged 70 years at baseline. For every 1.0 increase in BMI at age 70 years, AD risk increased by 36% in women but not men (1). In another survey, dementia risk was associated with an increased BMI (≥25.0) (2).

Patients with type 2 diabetes (an insulin resistance syndrome) and the ε4 allele have a higher risk of AD than those without ε4, which contributes to stabilize β-amyloid deposits (3). A baseline history of diabetes mellitus was associated with a subsequent decline in cognitive function in both men and women in the Cache County (Utah, United States) study (4). Among men, the risk was greatest among users of insulin (OR [odds ratio]: 4.45, 95% CI [confidence interval]: 2.00–9.90) and less among users of oral medications (OR = 1.51, 95% CI: 0.64–3.57) (4).

Recently, it was found in humans (5) that insulin infusion produced an increase in cerebrospinal fluid (CSF) insulin concentration and an increase in CSF beta-amyloid protein (Aβ 42) levels, most notably in older participants. Insulin infusion facilitated declarative memory, but such facilitation was attenuated in the participants with the greatest increase in CSF Aβ 42 levels. These findings that insulin may modulate Aβ 42 levels acutely in humans are consistent with recent in vitro studies on Aβ and support the hypothesis by Natalie Rasgon and Lissy Jarvik (6), more precisely in those with affective disorder already known as a risk factor for AD (6). Data from Framingham have previously shown that insulin treatment is associated with poorer performance in tests of verbal and visual memory (7).

Epidemiological studies of different sample populations have suggested that the risk of AD may be increased in individuals with high calorie diets (8). Dietary restriction can reduce neuronal damage and improve behavioral outcome in mouse models of AD (8). Animal studies have shown that the beneficial effects of dietary restriction result, in part, from increased production of neurotrophic factors and cytoprotective protein chaperones in neurons (8). Although further studies are required in humans, the emerging data suggest that high calorie diets and elevated insulin may render the brain vulnerable to neurodegenerative disorders. This phenomenon, however, may not be specific and limited to those with affective disorders, although older individuals with this condition appear to be a good target population with which to start intervention studies.

Only randomized multi-intervention studies will enable us to bring these new hypotheses, if they succeed in the field of clinical practice. These findings have important public health implications, and stress the importance of lifestyle and behavioral modifications. The prevention of obesity (or being overweight) and insulin resistance, even at advanced age, might be important in the prevention of dementia, the fastest-growing disease of late life.

Address correspondence to Bruno Vellas, Medecine Interne et Gerontologie Clinique, Pavillon J.P. Junod, C.H.U. Toulouse-Hopital de Casseleardit, 31059 Toulouse Cedex, France. E-mail: vellas.b@chu-toulouse.fr or vellasb@aol.com

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