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Exploring the Role of Insulin Resistance in neurodegenerative disorders: Insights from Clinical and Neuroimaging Analysis

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Abstract

Alzheimer's disease (AD) is a devastating neurodegenerative disorder (ND) characterized by progressive cognitive deficits, memory dysfunction, behavioral changes, and declines in decision-making functions. Emerging research has suggested a link between AD and brain insulin resistance (IR), which shares underlying biochemical, pathophysiological, and metabolic dysfunctions with diabetes mellitus (DM). Insulin and insulin-like growth factor type 1 (IGF-1) are notably expressed in brain regions susceptible to neurodegeneration, regulating neuronal and oligodendroglial cell survival, as well as neuronal plasticity. IR exacerbates oxidative stress by perturbing lipid and carbohydrate metabolism, impairing cell survival mechanisms, disrupting energy homeostasis, inducing mitochondrial dysfunction, and altering gene expression, ultimately leading to increased levels of phosphorylated-Tau and amyloid-β proteins in the brain. In this study, we sought to elucidate the associations between IR and ND such as AD. We conducted investigations on a cohort of patients presenting with suspected symptoms of both IR and ND. An extensive questionnaire was administered, capturing demographic information, disease status, family medical history, medication profiles, and disease progression history. Following rigorous inclusion and exclusion criteria, the patients were categorized into three distinct groups: IR, ND, and IR+ND. Blood samples were collected from each participant to evaluate glycemic status. Our findings revealed significant variations in serum glucose levels ($p<0.001$), particularly within the IR+ND group, where elevated levels were most pronounced. Conversely, serum insulin levels ($p<0.01$) exhibited significant reductions in the IR+ND group compared to the ND and IR groups. Notably, patients aged 40 years and above exhibited a heightened risk for both IR and ND compared to their younger counterparts. Neuroimaging via computerized tomography (CT) demonstrated distinctive features in ND patients, including widened sulci, increased extra-axial cerebrospinal fluid (CSF) space, moderate ventricular dilatation corresponding to cortical volume loss, and low attenuation areas in bilateral periventricular regions indicative of deep white matter ischemic changes. This research delves into the diverse spectrum of brain abnormalities associated with AD and investigates the potential role of IR in the progression of ND. Our findings underscore the significance of aberrant insulin signaling pathways in the pathogenesis of ND and the interplay between IR and cognitive decline. The observed variations in serum glucose and insulin levels within the IR+ND group suggest a complex relationship between metabolic dysfunction and neurodegeneration, warranting further investigation. Future research should explore the mechanistic links between IR and ND such as AD, focusing on molecular pathways and potential therapeutic interventions. Additionally, longitudinal studies tracking the progression of IR and its impact on ND development could provide invaluable insights. Moreover, personalized treatment strategies targeting insulin signaling pathways may hold promise in managing or delaying the onset of Alzheimer's disease in individuals at risk, particularly those with coexisting DM. This comprehensive study expands our understanding of the intricate relationship between IR and neurodegenerative disorders such as AD, shedding light on potential avenues for future research and therapeutic development.

Keywords: Alzheimer's Disease; Insulin Resistance; Glycemic Status; Neuroimaging; Cognitive Decline.

Ethical Approval: All the experimental protocols were followed according to approved guidelines of animal biosafety and rules of Institutional Biosafety committee of University of Agriculture (2875/ORIC), Faisalabad, Pakistan, and District Head Quarter Hospital Teaching Hospital (Ref. No. 4416/DHQ), Sargodha, Pakistan.