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Small molecule holds promise for detecting Alzheimer's disease at early stages

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Researchers from Federal University of Rio de Janeiro, Brazil, have established that high levels of a small molecule called D-serine associate with cognitive decline in Alzheimer's disease (AD). Their discovery may represent a novel and effective biomarker for AD.

D-serine is an amino acid, a class of molecules that may compose proteins or act independently to transmit physiological signals in the body. D-serine belongs to the subclass of D-amino acids, which do not often assemble into protein, but rather have important signaling functions. Indeed, senior author Rogerio Panizzutti and colleagues have been reporting that D-serine is present in the brain and acts as an essential signaling molecule at synapses, points of contact between neurons in which neuronal signals are propagated.

By looking at postmortem tissue from AD patients and matched controls, the team led by Dr. Panizzutti reports that D-serine is abnormally high in the hippocampus and cortex, brain regions severely affected in AD. They further found that increases in D-serine could be caused by the accumulation of amyloid-beta oligomers, toxins known to play a central role in AD.

Their main discovery, however, is that D-serine levels are elevated in the cerebrospinal fluid (CSF) of probable AD patients who already display early clinical symptoms. Currently, definite AD diagnosis is only possible after pathological investigation of postmortem brains, and the lack of an effective early AD biomarker precludes efforts to halt or

reverse disease progression.

Nevertheless, by combining data from cognitive assessment and CSF levels of the AD-linked amyloid-beta and tau levels, authors identified a group of patients likely suffering from AD. In those patients, CSF D-serine levels were clearly higher than in age-matched controls or patients affected by an unrelated disease. Furthermore, D-serine levels in the CSF correlated well with cognitive decline in probable AD patients, suggesting it could improve AD clinical prediction.

To test this possibility, authors Caroline Madeira and Rogerio Panizzutti included D-serine measurements in an amyloid-tau score (IATI) that has been proposed to assist in AD diagnosis. Incorporation of D-serine measures into IATI remarkably improved diagnostic sensibility and specificity, indicating that D-serine could be added to a panel of biomarkers aimed at early detection of AD. This work was led by Drs. Rogerio Panizzutti and Sergio T. Ferreira, and results appear online now in the journal *Translational Psychiatry*.

Although normal levels of D-serine are required for proper brain function, excessive D-serine levels may be harmful to the brain and contribute to AD. But perhaps more interesting is that this pilot study revealed that D-serine could go beyond its neuromodulatory functions and translate into clinical applications, serving as a potential AD biomarker. Further studies with larger cohorts are needed to replicate the findings and confirm this potential.

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