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Study reveals how non-alcoholic fatty liver disease causes Alzheimer's-like neuroinflammation

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Research from University of South Carolina associate professor Saurabh Chatterjee's laboratory in Environmental Health Sciences, Arnold School of Public Health, and led by Ayan Mondal, a postdoctoral researcher from the same lab, has revealed the cause behind the previously established link between non-alcoholic fatty liver disease (i.e., NAFLD, recently reclassified as metabolic associated fatty liver disease or MAFLD) and neurological problems. The link they discovered, the unique role of an adipokine (Lipocalin-2) in causing neuroinflammation, may explain the prevalence of neurological Alzheimer's disease-like and Parkinson's disease-like phenotypes among individuals with MAFLD.

The investigators, which include members of Chatterjee's Environment Health & Disease Laboratory and researchers from across UofSC, published their results in the *Journal of Neuroinflammation*, a pioneering journal in the field. These findings build on years of research conducted by the interdisciplinary team, which has unearthed previously unknown pathways and mechanisms between the liver and the gut microbiome with other parts of the body through their focus on how environmental toxins contribute to liver disease, metabolic syndrome and obesity.

MAFLD affects up to 25 percent of Americans and much of the global population—many of whom are unaware of their condition. Yet the effects of this silent disease are far-reaching, possibly leading to cirrhosis, liver cancer/failure and other liver diseases. The findings from

the current study not only confirm the strong correlation between MAFLD and neuroinflammation/neurodegeneration that has been established by other recent research, but it explains how this happens.

"Lipocalin 2 is one of the important mediators exclusively produced in the liver and circulated throughout the body among those who have nonalcoholic steatohepatitis—or NASH—which is a more advanced form of MAFLD," Chatterjee says. "The research is immensely significant because MAFLD patients have been shown to develop Alzheimer's and Parkinson's-like symptoms as older adults. Scientists can use these results to advance our knowledge in neuroinflammatory complications in MAFLD and develop appropriate treatments."

Ninety percent of the obese population and 40—70 percent of those with type 2 diabetes appear to have MAFLD, according to the Centers for Disease Control and Prevention. In addition to overweight/obese status and diabetes, other risk factors include high cholesterol and/or triglycerides, high blood pressure and metabolic syndrome.

These individuals have a higher risk for having diseased livers, which are associated with increased lipocalin 2—as found in the present study. The lipocalin 2 circulates throughout the body at higher levels, possibly inducing inflammation in the brain.

"Chronic neuroinflammation is a critical element in the onset and progression of neurodegenerative diseases, including Alzheimer's disease," says Prakash Nagarkatti, UofSC Vice President for Research and a member of the research team.

"Our study may help design new therapeutic approaches to counter the neuroinflammatory pathology in NASH but also in other related brain pathology associated with chronic inflammatory diseases," adds Chatterjee.

More information: Ayan Mondal et al, Lipocalin 2 induces neuroinflammation and blood-brain barrier dysfunction through liver-brain axis in murine model of nonalcoholic steatohepatitis, *Journal of Neuroinflammation* (2020). DOI: 10.1186/s12974-020-01876-4