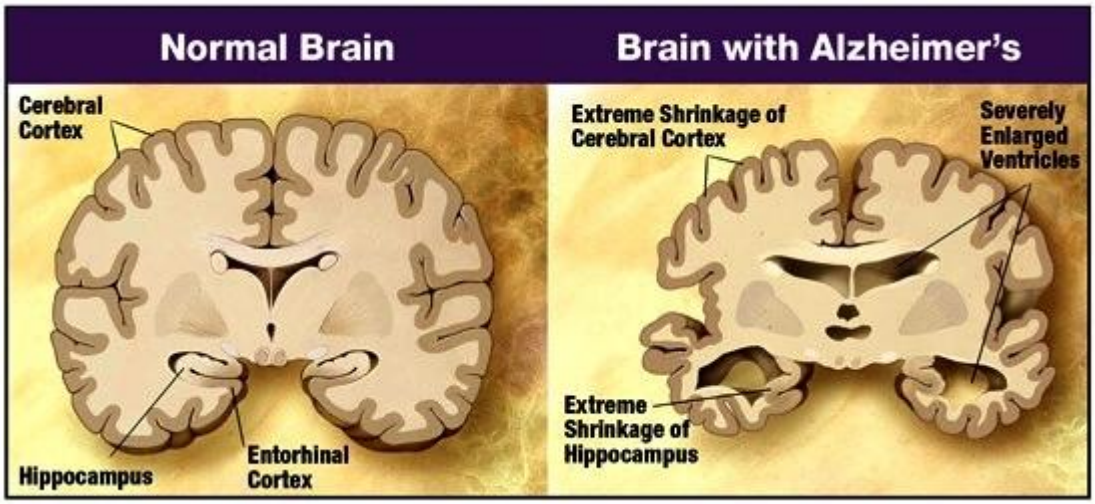
Alzheimer's disease (AD) is a progressive neurodegenerative disorder, characterized by senile plaques composed of amyloid-beta peptides and neurofibrillary tangles composed of hyperphosphorylated microtubule-associated tau proteins, which lead to brain atrophy. Investigations of the mechanisms underlying AD pathogenesis indicated the accumulation of amyloid-beta peptides, chronic neuroinflammation, tau pathology, and irreversible neuron loss. Korean researchers investigated the possible link between COVID vaccination and the onset of Alzheimer's disease and its prodromal stage, mild cognitive impairment (MCI), in this nationwide retrospective cohort study. They evaluated a large sample size of COVID-vaccinated participants without long COVID syndrome, a new disease that develops after severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) infection. Long COVID syndrome encompasses a wide range of organ dysfunction and clinical symptoms, but the most frequent, persistent, and disabling symptoms of long COVID are neurological.

Interestingly, in 2021, Yapici-Eser et al. hypothesized that mimicry between human proteins and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proteins may have a role in neurobiological pathways that underlie the neuropsychiatric manifestations of COVID-19 and long COVID syndrome. They utilized a computational methodology (Host-Microbe Interaction PREDiction Algorithm) to detect mimicry between human proteins and SARS-CoV-2 proteins and classified these interactions according to the molecular paths of COVID-19-associated neuropsychiatric symptoms. The results showed that SARS-CoV-2 proteins mimic 17 proteins linked with Alzheimer's disease-amyloid secretase pathway and 25 proteins linked with Alzheimer's disease-presenilin pathway, like beta-secretase, presenilin-1, amyloid-beta precursor and gamma-secretase subunit-2. (Yapici-Eser et al. Neuropsychiatric Symptoms of COVID-19 Explained by SARS-CoV-2 Proteins' Mimicry of Human Protein. Front Hum Neurosci 2021 15:656313.) https://www.frontiersin.org/journals/human-neuroscience/articles/10.3389/fnhum.2021.656313/full



About the study

To assess the incidence of AD and MCI following COVID immunization, this retrospective cohort study analyzed data from Seoul residents, randomly selected from the Korean National Health Insurance Service (NHIS), who accounted for half of the city's population as of 1 January 2021, before the Omicron pandemic.

To assess the link between COVID immunization and the onset of specific diseases, medical records from a year before the index date were reviewed, and participants with any record of the pertinent diseases during this period were excluded. The onset of the diseases was marked by a primary or secondary diagnosis after the index date. Diseases were categorized according to the International Classification of Diseases, 10th Revision (ICD-10), and included MCI, AD, vascular dementia, other forms of dementia, Parkinson's disease (PD), neurodegenerative disorders, cranial neuropathy, autonomic dysfunction, insomnia, and obesity.

Participants were categorized into four groups according to their vaccination status: unvaccinated, mRNA vaccine only, cDNA vaccine only, and a combination of the two. The mRNA vaccine-only group received two doses of the Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) vaccines, while the cDNA vaccine-only group received two doses of the Oxford-AstraZeneca (ChAdOx1 nCoV-19) or Johnson & Johnson (Ad26.COV2-S) vaccines. A heterologous vaccine group consisted of individuals vaccinated with both mRNA and

cDNA vaccines.

Results

The study analyzed data from a 50% sample of Seoul, South Korea, residents (4,348412 Seoul residents), randomly selected from the NHIS. Inclusion criteria were limited to individuals who had received both doses of the COVID-19 vaccine by September 30, 2021. Those who did not receive their second dose by this deadline were omitted. Ultimately, 558,017 individuals aged 65 or older (519,330 vaccinated and 38,687 unvaccinated) were included in the analysis.

The findings showed an increased incidence of MCI and AD in COVID-vaccinated individuals, particularly those receiving mRNA vaccines, within three months post-vaccination. The mRNA vaccine group exhibited a significantly higher incidence of AD and MCI than the unvaccinated group. Individuals who received cDNA vaccines only and cross-vaccination also exhibited a significant increase in MCI incidence compared to those unvaccinated. The authors noted that this increase was observed as early as 12 weeks after mRNA vaccination, suggesting its potential temporal association with the onset of the Alzheimer's disease continuum.

There was no significant association between the COVID-19 vaccination and the

development of vascular dementia, or PD.

Conclusion

The authors suggested several mechanisms that could provide additional insights into the long-term effects of mRNA vaccines on the central nervous system and their potential link to neurodegenerative diseases, including AD. The mRNA encoded in the SARS-CoV-2 vaccine is known to cross the blood-brain barrier, or at least disrupt the barrier, thus, the SARS-CoV-2 spike protein might interact with amyloid-beta proteins, affecting their aggregation and influencing microglial activation. Lipid nanoparticles in the mRNA vaccines can activate Toll-like receptors, leading to inflammatory reactions that might exacerbate neuroinflammatory pathways associated with AD pathogenesis. A cascade of low-level neuroinflammatory responses, induced by vaccines, is a known contributor to the development and progression of neurodegeneration. In addition, N1-methyl pseudouridine in mRNA vaccines may cause ribosomal frameshifting during translation, resulting in aberrant protein products that could contribute to neurodegenerative processes.

The authors emphasized the strength of the study's large sample size. They concluded that this study suggests a potential link between COVID-19 vaccination, particularly mRNA vaccines, and increased incidences of AD and MCI, underscoring the need for further research. Future studies with longer follow-up periods should elucidate the relationship between vaccine-induced immune responses and neurodegenerative processes, advocating for an investigation into the vaccines' long-term neurological impacts.

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Journal Reference

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