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Researchers pinpoint molecular signature of post-stroke depression

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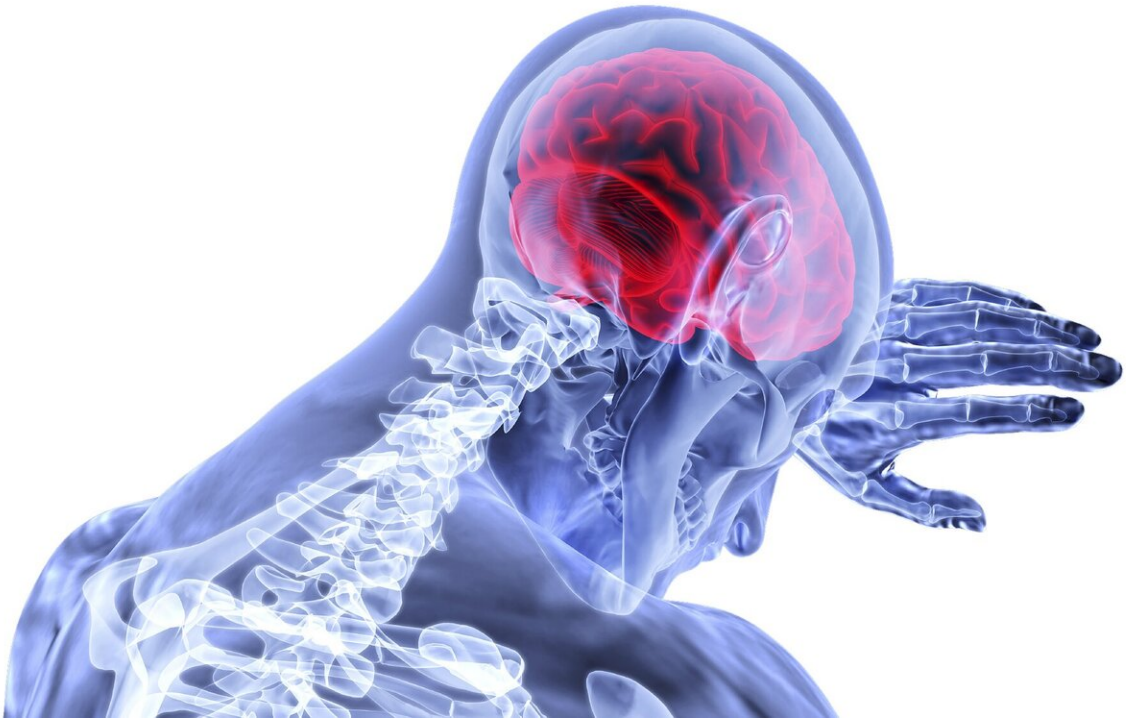

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Earlier in 2023, Pennsylvania Senator John Fetterman checked himself into a hospital for clinical depression after suffering a near-fatal stroke. Fetterman's case of post-stroke depression may be one of the most newsworthy, but it is far from rare: Around a third of all survivors develop depression.

Now, Stanford Medicine researchers have made inroads into understanding the link between stroke and depression. Using blood samples from 85 adults who had suffered a stroke, the scientists pinpointed a molecular signature of post-stroke depression. Many of the molecules seen in the blood of stroke survivors with depression were immune molecules, suggesting a link between immune activity in the brain and post-stroke depression.

The findings were published in *Brain, Behavior, and Immunity*.

"We can now look at a stroke survivor's blood and predict their mood," said Marion Buckwalter, MD, Ph.D., a professor of neurology and of neurosurgery and a senior author of the paper. "This means there is a genuine association between what's happening in the blood and what's happening with a person's mood. It also means that, down the road, we may be able to develop new treatments for post-stroke depression."

More than stress

Despite the high number of stroke survivors who become depressed in the months and years after suffering a stroke, scientists have been unsure how stroke and mental health are linked. In some instances, having a stroke could set off stress-induced depression.

"There are certainly psychological impacts of stroke, and it's not unusual for stroke survivors to have new stressors, like the worry about having another stroke or the burden on caregivers," Buckwalter said.

But studies have shown that rates of depression are far higher in older people after a stroke than after other debilitating injuries. This hints at something else happening in the brain, and researchers have theorized that changes triggered by a stroke could make patients more prone to depression.

In the new study, postdoctoral scholars Neda Bidoki, Ph.D., Kristy Zera, Ph.D., and Huda Nassar, Ph.D.—the co-lead authors of the paper—analyzed blood samples from 85 volunteers being treated for stroke at Stanford Medicine. All participants had suffered a stroke at least five months before the study and volunteered their time to provide information on their mood, emotional functioning and physical stroke symptoms. About one in five had a diagnosis of depression, and the same number were taking prescription antidepressants.

The researchers measured levels of 1,196 different proteins in the blood samples. Then, a group in the laboratory of Nima Aghaeepour, Ph.D., an associate professor of anesthesiology, perioperative and pain medicine who is the study's co-senior author, used machine learning approaches to discover patterns in the data linking the blood proteins to mood.

"While no individual proteins were completely predictive of patients' post-stroke depression, a specific set of about 1,000 proteins—when considered together, along with people's ages and the time since their stroke—could predict whether patients were likely to have depression at any time after a stroke," Aghaeepour said.

The researchers identified around 200 proteins in the blood that had the greatest association with post-stroke depression; although none could individually predict depression, scientists saw significant changes to the levels of these proteins in patients with depression. Nearly half of these proteins had been identified in previous studies as having altered levels in non-stroke-related depression.

When the researchers looked more closely at the proteins' functions, they found that many were known to play a role in the immune system, and most of those were seen at higher, rather than lower, levels in people with depression. This suggests that an overactive immune response —perhaps triggered by stroke—could be a hallmark of post-stroke

depression. (Some studies have also suggested this for non-stroke related depression.)

The researchers used their data as well as information from previous studies to assemble a model of how the immune response following a stroke could change both serotonin—a chemical messenger that plays a role in mood—and plasticity, or the process by which the brain constantly rewires itself. These two changes could contribute to depression, Buckwalter said.

More work is needed to confirm the underlying cause of post-stroke depression, but if the immune response and serotonin pathways do play a role, it suggests new paths to possible treatments, Buckwalter added.

"There are already antidepressant treatments that work for some patients, and I encourage anyone who has had a stroke and is feeling depressed to get help," she said. "In the future, if we can really figure out the biological underpinnings of post-stroke depression, I hope we have even more effective treatments."

More information: Neda H. Bidoki et al, Machine learning models of plasma proteomic data predict mood in chronic stroke and tie it to aberrant peripheral immune responses, *Brain, Behavior, and Immunity* (2023). DOI: 10.1016/j.bbi.2023.08.002

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