Study ties immune cells to delayed onset of post-stroke dementia

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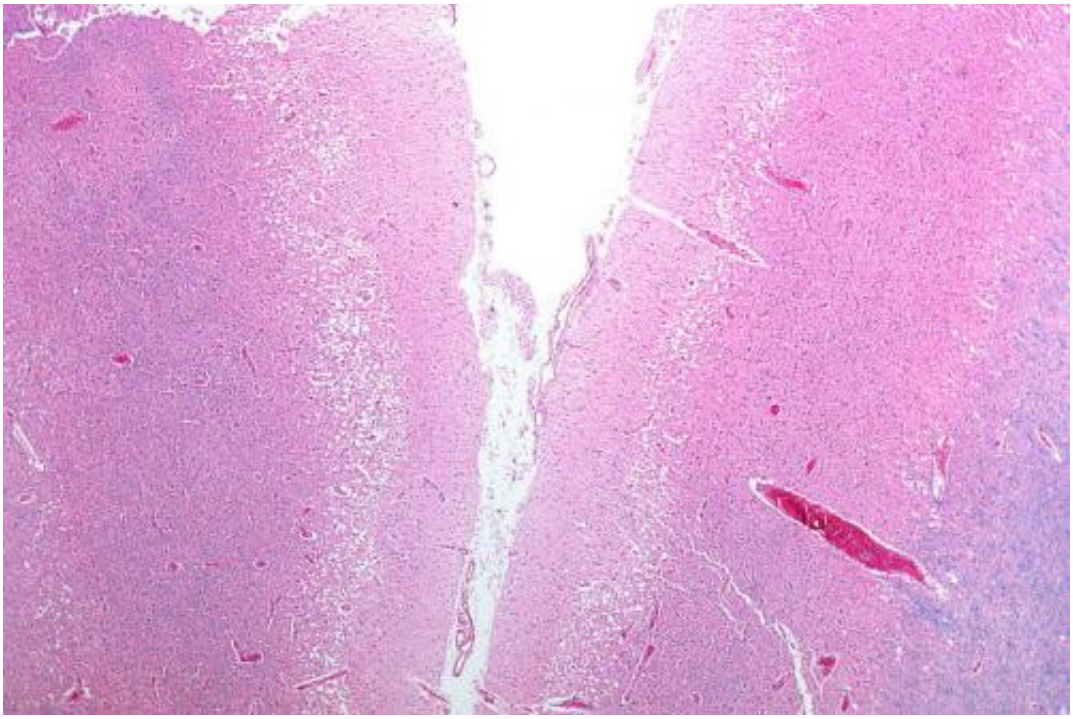

Micrograph showing cortical pseudolaminar necrosis, a finding seen in strokes on medical imaging and at autopsy. H&E-LFB stain. Credit: Nephron/Wikipedia

A single stroke doubles a person's risk of developing dementia over the following decade, even when that person's mental ability is initially unaffected. Why this delayed deterioration occurs has been a mystery. Now, Stanford University School of Medicine investigators think they have discovered a major reason for it.

In experiments using both mouse models of stroke and brain-tissue samples from humans, they linked the delayed onset of post-stroke dementia to the persistent presence, in the brain, of specialized immune cells that shouldn't be there at all.

The discovery could potentially translate into ways of identifying people at risk for dementia, allowing physicians time to try to stave off the disease. Drugs that can disable these immune cells are already available.

At roughly 800,000 new cases per year, stroke is the second-biggest cause of serious long-term disability in the United States, generating $74 billion annually in treatment and caretaking costs. Of the 7 million living stroke survivors nationwide, one-third either suffers from dementia, or will.

In a study to be published Feb. 4 in *The Journal of Neuroscience*, a team directed by Marion Buckwalter, MD, PhD, assistant professor of neurosurgery and of neurology and neurosciences, examined several mouse models of stroke, as well as human brain-tissue samples, and found strong evidence that antibody-producing cells called B cells play a key role in the delayed onset of dementia. Buckwalter is the study's senior author. The lead author is former postdoctoral scholar Kristian Doyle, PhD.

B cells help, usually

The antibodies that B cells produce are normally of great value to us. They circulate throughout blood and lymph, and bind to microbial invaders, gumming up the pathogens' nefarious schemes and marking them for destruction by other immune cells. Occasionally, B cells wrongly begin generating antibodies that bind to the body's own healthy tissues, causing certain forms of autoimmune disease, such as rheumatoid arthritis. Rituxan, a drug approved by the Food and Drug

Administration for this condition, is actually an antibody itself: Its target is a protein found on the surface of every B cell. Use of this drug depletes B cells in the body, relieving the symptoms of rheumatoid arthritis and other B-cell-mediated disorders.

Like almost all other types of immune cells, B cells are virtually nonexistent in the brains of healthy people, whose outermost ramparts are mostly impervious to the cells and large molecules (like antibodies) freely circulating elsewhere. But the blood-brain barrier is not entirely unbreachable and is rendered much more permeable upon brain damage.

Two small reports from the last decade mentioned the puzzling presence of substantial numbers of immune cells in about 50 percent of the autopsied brains of people who had suffered strokes. This led Buckwalter to look more closely at the phenomenon.

Buckwalter is a team leader of Stanford's Stroke Collaborative Action Network, which is part of the Stanford Neurosciences Institute and coordinates stroke research efforts throughout the university. She was intrigued by those reports. So she and her colleagues embarked on a series of experiments in mouse models of stroke. Buckwalter's group fine-tuned their experimental procedures so that brain structures central to cognition in the mice would initially be left intact after a stroke.

"When we looked at the brains of these mice one week post-stroke, we saw a negligible presence of B cells in the stroke core," Buckwalter said. "But at seven weeks out, there were tons of them." The presence of B cells persisted at 12 weeks. The cells tended to cluster in or near the stroke core, where normal brain cells that succumbed to stroke-induced oxygen deprivation had died. No such B-cell infiltration was evident in the brains of mice subjected to a sham procedure in which their brains experienced no stroke.

The scientists also determined that the B cells had been actively producing antibodies and progressing through various stages of development that typify such cells once they've been activated by exposure to foreign material.

Drug stems cognitive loss

In tests of the mice's ability to store short-term memory—a key yardstick in assessing dementia—mice in which a stroke had been induced performed about as well a week later as mice in the control group did, indicating that key brain structures in the post-stroke mice were as yet unharmed. But by seven weeks, the post-stroke mice had developed substantial memory deficits. Mice in the control group hadn't.

When Buckwalter and her associates performed their experiments on post-stroke mice that were genetically altered to be incapable of generating B cells, they suffered no such delayed cognitive impairment.

So the investigators repeated their set of experiments on the same normal laboratory mice strain they'd previously been working with—except that this time, beginning five days after stroke was induced and continuing biweekly for several weeks, the mice were given a mouse analog of Rituxan to deplete their B cells. This time, the post-stroke mice exhibited no signs of delayed cognitive loss.

Finally, the Stanford scientists examined autopsied brain sections from stroke cores of 21 stroke patients, all of whom had dementia. Among these, 12 contained suspiciously high numbers of B cells.

To see if a prominent B-cell presence in the brain might be a common occurrence in old age, even among healthy people, they looked at brain samples from nine age-matched patients with no history of stroke or dementia. In these brains, B cells were rare.

More work needed for a therapy

Buckwalter speculated that B cells entering a brain rendered accessible by a stroke may, upon exposure to intercellular substances released by dead or dying cells, become reactive to brain tissue, setting off a spiraling cycle of spreading cell injury and further B-cell activation. It's likely that this happens in only a fraction, albeit possibly a substantial one, of stroke patients, she cautioned, so it would be medically unsound to simply dose all stroke patients with a B-cell-depleting drug. But she suggested that a brain-penetrating, B-cell-tagging compound or antibody that was labeled for detection by, say, MRI could help identify candidates for such a therapy.

"We're not there yet. Much more work needs to be done to nail down who this happens to and what's the right drug timing and dosage," Buckwalter said. "But it's exciting to think that delayed-onset post-stroke dementia, which carries such an enormous cost to individuals and to society, is potentially treatable."

Provided by Stanford University Medical Center