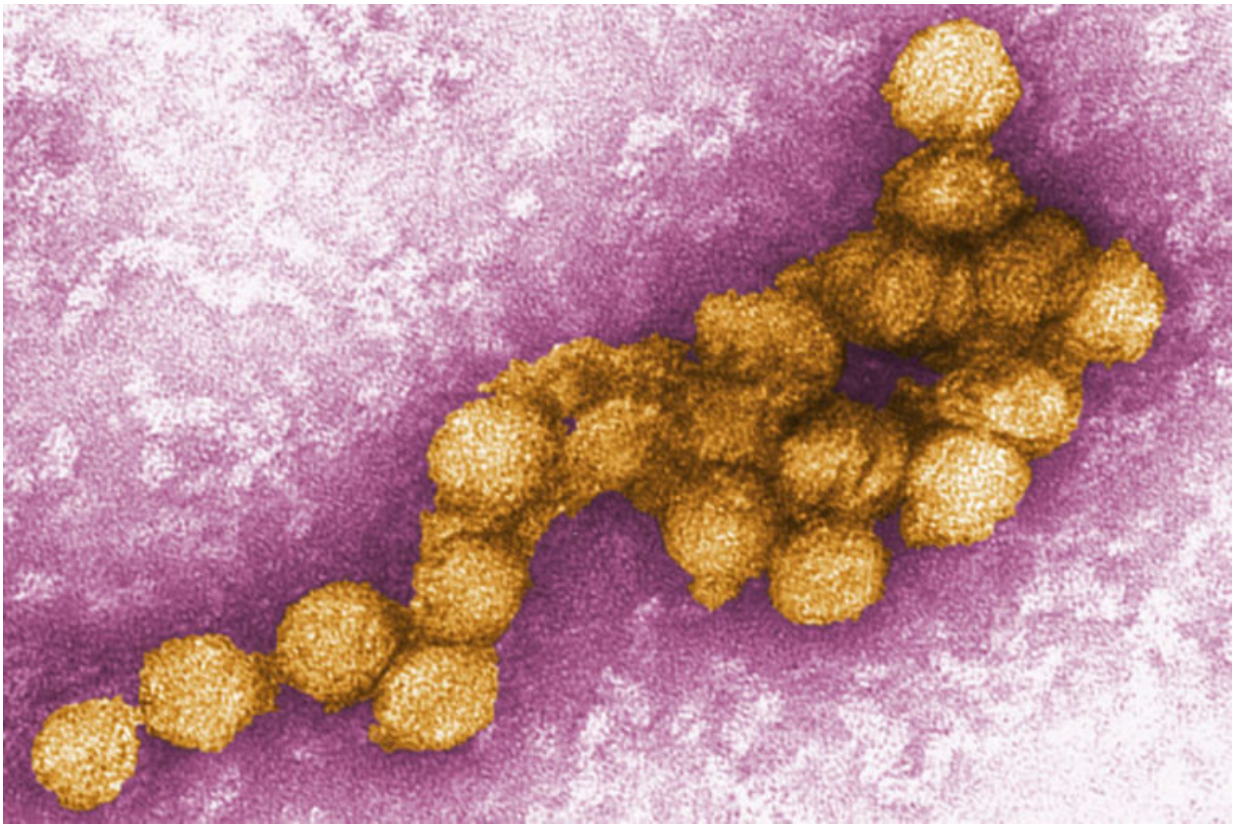
Memory loss from West Nile virus may be preventable

January 15 2018, by Tamara Bhandari



People who survive brain infection with West Nile virus (pictured) can have neurological problems long after the virus is gone. A new study in mice suggests that such ongoing problems may be due to unresolved inflammation that hinders the brain's ability to repair damaged neurons and grow new ones. Reducing inflammation with an arthritis drug protected mice from West Nile-induced memory loss. Credit: CDC

More than 10,000 people in the United States are living with memory loss and other persistent neurological problems that occur after West Nile virus infects the brain.

Now, a new study in mice suggests that such ongoing neurological deficits may be due to unresolved inflammation that hinders the brain's ability to repair damaged neurons and grow new ones. When the inflammation was reduced by treatment with an arthritis drug, the animals' ability to learn and remember remained sharp after West Nile disease.

"These memory disturbances make it hard for people to hold down a job, to drive, to take care of all the duties of everyday life," said senior author Robyn Klein, MD, Ph.D., a professor of medicine at Washington University School of Medicine in St. Louis. "We found that targeting the inflammation with the arthritis drug could prevent some of these problems with memory."

The findings are available online in *Nature Immunology*.

Spread by the bite of a mosquito, West Nile virus can cause fever and sometimes life-threatening brain infections known as West Nile encephalitis. About half the people who survive the encephalitis are left with permanent neurological problems such as disabling fatigue, weakness, difficulty walking and memory loss. These problems not only persist but often worsen with time.

Klein and colleagues previously had shown that during West Nile encephalitis, the patient's own immune system destroys parts of neurons, leading to memory problems.

"We started wondering why the damage isn't repaired after the virus is cleared from the brain," said Klein, vice provost and associate dean for

graduate education for the Division of Biology & Biomedical Sciences. "We know that neurons are produced in the part of the brain involved in learning and memory, so why weren't new neurons being made after West Nile infection?"

To find out, Klein; co-first authors Michael Vasek, a postdoc researcher, and graduate research assistant Charise Garber; and colleagues injected mice with West Nile virus or saltwater. During the acute infection, the mice received several doses of a chemical compound that tags neural cells as they are formed. Forty-five days after infection, the researchers isolated the tagged cells from the mice's brains and assessed how many and what kinds of cells had been formed during the first week of infection.

Mice ill with West Nile disease produced fewer neurons and more astrocytes – a star-shaped neural cell – than uninfected mice. Astrocytes normally provide nutrition for neurons, but the ones formed during West Nile infection behaved like immune cells, churning out an inflammatory protein known as IL-1.

IL-1 is an indispensable part of the body's immune system. It is produced by immune cells that swarm into the brain to fight invading viruses. Once the battle is won, the immune cells depart and IL-1 levels in the brain fall.

But in mice recovering from West Nile infection, astrocytes continue to produce IL-1 even after the virus is gone. Since IL-1 guides precursor cells down the path toward becoming astrocytes and away from developing into neurons, a vicious cycle emerges: Astrocytes produce IL-1, which leads to more astrocytes while also preventing new neurons from arising.

Hampered by an inability to grow new neurons, the brain fails to repair

the neurological damage sustained during infection, the researchers said.

"It's almost like the brain gets caught in a loop that keeps IL-1 levels high and prevents it from repairing itself," said Klein, who is also a professor of neuroscience and of pathology and immunology.

To see whether the cycle could be broken, Klein and colleagues infected mice with either West Nile virus or saltwater as a mock infection. Ten days later, they treated both groups of mice with a placebo or with anakinra, an FDA-approved arthritis drug that interferes with IL-1.

After giving the mice a month to recover, they tested the animals' ability to learn and remember by placing them inside a maze. Mice that had been infected with West Nile virus and treated with a placebo took longer to learn the maze than mock-infected mice. Mice that were infected and treated with the IL-1 blocker learned just as quickly as mock-infected mice, indicating that blocking IL-1 protected the mice from memory problems.

"When we treated the mice during the acute phase with a drug that blocks IL-1 signaling, we prevented the memory disturbance," Klein said. "The cycle gets reversed back: They stop making astrocytes, they start making new neurons, and they repair the damaged connections between neurons."

But, Klein cautions, IL-1 itself may not be a good drug target for people because of the important role it plays in fighting viruses. Suppressing IL-1 while the virus is still in the brain could exacerbate encephalitis, already a potentially lethal condition.

"This is a proof of concept that a drug can prevent cognitive impairments caused by viral encephalitis," Klein said. "This study sheds light on not just post-viral memory disturbances but other types of

memory disorders as well. It may turn out that IL-1 is not a feasible target during viral infections, but these findings could lead to new therapeutic targets that are less problematic for clearing virus or to therapies for neurologic diseases of memory impairment that are not caused by viruses."

More information: Charise Garber et al. Astrocytes decrease adult neurogenesis during virus-induced memory dysfunction via IL-1, *Nature Immunology* (2017). DOI: 10.1038/s41590-017-0021-y

Provided by Washington University School of Medicine in St. Louis