Distinct AIDS viruses found in cerebrospinal fluid of people with HIV dementia

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When the virus that causes AIDS infects the central nervous system, it can lead to the development of a severe neurological disease called HIV-associated dementia (HAD).

The advent of highly active antiretroviral therapy, or HAART, has helped reduce HAD. But some studies show that HAART may not offer complete protection from less severe HIV-associated neurological problems, nor might it always help to reverse it. As people live longer with AIDS, their risk of developing neurological problems may increase.

New research for the first time may have pinpointed a possible explanation for the problem, one that might also help predict who is at greatest risk for HAD.

Scientists led by researchers from the University of North Carolina at Chapel Hill School of Medicine have discovered that some people diagnosed with HAD have two genetically distinct HIV types in their cerebrospinal fluid (CSF), the clear fluid found in the spaces around and inside the brain and spinal cord. What's more, these variants are not detected in HIV circulating in the blood, and one of them could be present years before the onset of dementia. The detection of these viruses in the CSF is evidence that they are growing in the central nervous system.

In a study published October 6, 2011 in the journal, PloS Pathogens, one of the two HIV variants found in CSF reproduces in immune system T

cells, as does the virus growing in the blood. But the other type does not. It infects and replicates in macrophages, another white immune cell that engulfs and digests foreign material, including bacteria.

"This is the first time that anyone has demonstrated active replication of HIV virus in a cell type other than T cells," said study senior author Ronald Swanstrom, PhD, professor of biochemistry and biophysics and director of the UNC Center for AIDS Research.

During their own clinical investigations, Swanstrom's current collaborators, neurologists Richard R. Price, MD and Serena Spudich, MD, at the University of California, San Francisco had been collecting blood and CSF samples from patients who had either HIV-associated dementia or other severe neurological defects. Samples were collected with written informed consent from the patients' families. These were the samples used for the current study.

"After the start of therapy, we looked at the rate at which the virus disappeared," Swanstrom said. "We know that HIV in the blood disappears quickly when you go on therapy, and that's because the virus is growing in T cells, which have a very short half-life," the period of time it takes for a substance undergoing decay to decrease by half. Infected T-cells decay by half every one to two days

But for half of the patients in the new study, HIV growing in the cerebrospinal fluid decayed very slowly, several weeks to one month. "This is evidence the virus is actually being produced by a cell with a longer half-life, and not a T-cell," Swanstrom said.

The researchers also found that the slow-decaying HIV had a particular attraction, or "tropism," to macrophages and were able to infect them.

"Those viruses are known to exist in autopsy brain studies. It has been

known for ten years that a subset of HIV-infected patients have slow decay of the virus in the CSF, and it's also been known for a long time that you can find macrophage-tropic virus in the brain," Swanstrom said. "But no one has ever brought the two together in a way that makes sense and could give you a tool to evaluate what's going on the brain by looking at cerebrospinal fluid."

The study also found HIV-infected macrophages present in a CSF sample two years before the patient was diagnosed with dementia. Swanstrom said this tells us there's information in the CSF that potentially could predict disease progression. "Is it bad to have these viruses around even if you don't get a diagnosis of dementia? And are they potentially causing cognitive damage that can be reversed with HAART?"

To explore these and other questions, Swanstrom and Price of UCSF again will collaborate under a 5-year, $3 million grant from the National Institute of Mental Health to expand the research in HIV patients who don't have dementia and are starting therapy. The new study will look for biomarkers in the CSF in the form of HIV variants or other immune protein information that may predict improvement, stability or decrease in cognitive capacity during therapy.

In the new project, Swanstrom's UNC team will include Joseph J. Eron, MD, professor of medicine and Director of the UNC Center for AIDS Research Clinical Core, Kevin Robertson, PhD, clinical psychologist in the department of neurology, and Angela Kashuba, PharmD, associate professor, Eshelman School of Pharmacy and director, UNC Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Core.

People infected with HIV sometimes delay going on HAART, Swanstrom said. "Our research will help further understand what's going on in the central nervous system of patients who are still alive and in

tissue that's accessible in the clinical setting, i.e. CSF. If these individuals knew there was an AIDS virus replicating independently in their CNS, it might affect their decision when to start treatment with HAART."

Provided by University of North Carolina