HIV-Weakened Blood-Brain Barrier Could Help Explain Cognitive Problems

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An expert team of neuroscientists has discovered that HIV weakens the blood-brain barrier that keeps infectious diseases and harmful chemicals from entering and damaging the brain. The study, to be published in the June 29 issue of *The Journal of Neuroscience*, could help explain why some people experience cognitive problems despite having undetectable viral loads from antiretroviral (ARV) therapy.

Since HIV's discovery in the early 1980s, people with HIV have been contending with the virus's harmful effects on the brain. In those early days, and for more than a decade thereafter, people frequently came down with serious brain problems such as severe dementia and meningitis. Since the introduction of potent combination ARV therapy in the late 1990s, the incidence of more severe brain disease has diminished considerably; however, challenges remain—even in people with high CD4s who have their virus in check.

In the past couple of years, several research teams have confirmed that rates of mild cognitive decline and peripheral nerve damage are still occurring at much higher rates in HIV-positive people than in the general public. In fact, one study found that perhaps half of all people with HIV have at least some cognitive defects, although the symptoms are generally so mild that most people aren't even aware of them. What's more, the brain damage and inflammation that HIV brings apparently occur even in people whose virus levels in the blood are undetectable.

To better explain why this occurs, Eliseo Eugenin, PhD, from the Albert Einstein College of Medicine in New York City, and his colleagues have been studying a type of brain cell known as an astrocyte for several years. Astrocytes, which are neural cells that can live inside blood vessels near the brain, help the blood-brain barrier function properly. In a 2007 paper, Eugenin's team documented the fact that up to 5 percent of astrocytes in this region are infected with HIV, though it is not yet clear how many are infected in people taking ARVs; however, even this finding couldn't totally explain the ongoing brain damage that other studies have found in these people.

Eugenin and his colleagues next looked at the signaling molecules that astrocytes use to communicate with other astrocytes. These chemicals, called gap junctions, help the astrocytes work with epithelial cells lining blood vessels to let in molecules that are helpful to the brain, while filtering out those that are harmful. Specifically, Eugenin's team created an artificial model of the blood-brain barrier and then recorded the astrocytes' health and ability to function.

The team found that the HIV in those 5 percent of infected cells caused considerable damage to neighboring astrocytes—likely through releasing toxic chemicals—and that the neighboring astrocytes eventually died off. To confirm whether this die-off, and the resulting damage to the blood-brain barrier, could happen in the real world, Eugenin's team looked at a similar process in macaque monkeys infected with the monkey version of HIV. It turned out that the infected astrocytes in the monkeys' brains caused similar damage to surrounding astrocytes.

"Researchers have been stymied to explain why HIV-associated neurological complications persist, despite potent combination antiviral therapies that have dramatically improved health and survival," said Igor Grant, MD, an expert at the University of California at San Diego who studies HIV-related brain damage, in a release published by Eurekalart. "This study provides a possible explanation indicating that minute numbers of infected astrocytes can trigger a cascade of signals that could open the brain to various toxic influences."

Now that researchers are aware of the toxic effects of infected astrocytes, it is hoped that new drugs could be found to block the harmful chemical transmissions from those infected cells and help keep the blood-brain barrier intact.
