Potential Cause of HIV-Related Depression, Cognitive Problems Discovered

July 11, 2012

Researchers at Georgetown University Medical Center believe they have discovered a cause of depression and dementia-like symptoms in people living with HIV, according to a paper published in the July 11 issue of the Journal of Neuroscience. The authors suggest the finding not only has therapeutic potential, but may also provide a way to test people living with HIV to determine their risk for developing depression and cognitive problems.

Under the direction of Italo Mocchetti, MD, of the university's department of neuroscience, the scientific team found that HIV interferes with the brain's production of a protein growth factor that neurons need in order to function correctly. This can lead to psychological and cognitive problems, such as those involving memory, learning and motor function.

"We believe we have discovered a general mechanism of neuronal decline that even explains what happens in some elderly folks," says Mocchetti in a news announcementaccompanying the publication of the paper. "The HIV-infected patients who develop this syndrome are usually quite young, but their brains act old."

In the mid to late 1980s, up to half of all people with HIV eventually developed debilitating dementia or a serious brain-related infection. Fortunately, this is no longer true, at least not in countries where potent antiretroviral therapy is widely available.

Today, HIV-associated dementia (known as HAD or AIDS dementia complex, ADC) is rarely diagnosed. However, recent evidence suggests that even when HIV levels are undetectable in the blood, the virus is still affecting people's brains—which can lead to mild-to-moderate cognitive problems now classified as HIV-associated neurocognitive disorder (HAND).

Estimates on the prevalence of HAND vary. In one large study, up to 50 percent of people were diagnosed with HAND—the vast majority with asymptomatic or mild impairment—though other studies have found rates as low as 15 percent. HAND appears to be more common in older people, people coinfected with HIV and hepatitis C, those with cardiovascular disease (CVD) and those who've been HIV positive for a long time. People with uncontrolled HIV also appear to have higher rates of HAND than people with undetectable HIV levels.

The latest findings out of Georgetown are the product of years of work. It began when Mocchetti and his colleagues were given a grant from the National Institute on Drug Abuse to determine whether there was a connection between dementia in people living with HIV and the use of cocaine and morphine.

They found that it was the virus that was responsible for the dementia, not the drugs, and so they set out to discover how the virus was altering neuronal function.

Their scientific break came when the researchers were able to study the blood of 130 women who were enrolled in the Women's Interagency HIV Study (WIHS). In a paper published last year, Mocchetti and his colleagues reported that among women with low levels of the mature brain-derived neurotrophic factor (mature BDNF) in blood samples, there was a higher risk of developing brain abnormalities.

The most recent Journal of Neuroscience paper took things one step further. The researchers looked at the effects of HIV on rat neurons and in postmortem brain samples from people with HIV. Here, too, the researchers confirmed an association between cognitive problems and low BDNF levels, particularly in the brain samples taken from donors who reported symptoms of dementia or HAND while alive.

Mocchetti's group then worked out the role BDNF might play in the onset of cognitive problems.

Normally, neurons release a long form of BDNF known as proBDNF. Then certain enzymes, including one called furin, cleave proBDNF to produce mature BDNF, which then nurtures brain neurons. When uncut, proBDNF is toxic, leading to "synaptic simplification," or the shortening of axons used by neurons to connect to each other.

According to their Journal of Neuroscience paper, Mocchetti's team found that HIV's gp120—a protein on the virus's surface—interferes with the normal process of cleaving proBDNF, resulting in neurons primarily secreting a toxic form of BDNF. The same imbalance between mature BDNF and proBDNF occurs as we age, the authors explain, although no one knows how that happens.

"The link between depression and lack of mature BDNF is also known, as is the link to issues of learning and memory," Mocchetti says. "That's why I say HIV-associated dementia resembles the aging brain."

The findings suggest a possible therapeutic intervention, he adds. "One way would be to use a small molecule to block the receptor that proBDNF uses to kill neurons. A small molecule like that could get through the blood-brain barrier. The finding also suggests that measuring proBDNF in people living with HIV may provide a biomarker of risk for developing dementia.

"This finding is extremely important for both basic scientists and physicians," Mocchetti says, "because it suggests a new avenue to understand, and treat, a fairly widespread cause of dementia."

© 2026 Smart + Strong All Rights Reserved.
http://beta.docker.poz.com/article/hiv-dementia-bdnf-22682-6556