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A tale of two diseases

Aging HIV patients inspire a closer look at Alzheimer's disease

By Shraddha Chakradhar

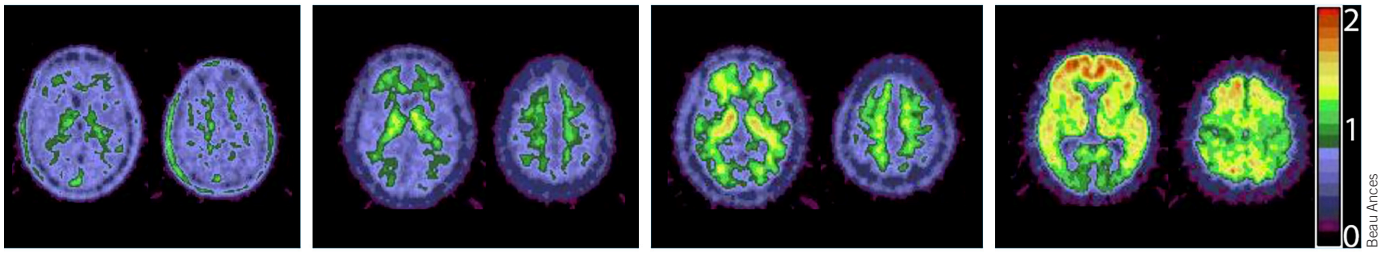
In the early days of the AIDS epidemic, there was little to stop the disease from ravaging the central nervous system of patients with the illness. HIV-associated dementia was commonly seen in infected people, as were cases of encephalitis and some forms of neurocognitive impairment. All these neurological symptoms collectively became known as HIV-associated neurocognitive disorder (HAND). The development of therapy against HIV not only drastically reduced the number of HIV deaths, but also reduced the number of people suffering severe forms of HAND. Today, about 30%–50% of HIV-infected individuals on treatment in the US still suffer from HAND, but most of these cases are less severe forms of the condition. Now, some scientists are seeking to understand whether HIV might pave the way to other forms of cognitive decline, namely Alzheimer's disease.

This possible connection began to interest memory specialist Scott Turner when he met with a 71-year-old HIV-positive attorney in the Washington, DC, area four years ago. The patient reached out to Turner and complained that he had decided to retire because of his inability to remember details of his legal cases well enough. The man's regular physician had attributed the memory problems to a mild form of HAND, but to Turner, it seemed more serious. "This person had to stop working," says Turner, director of Georgetown University's Memory Disorders Program. "If someone had to stop working, I would not call that mild."

The patient came to Turner searching for the true culprit behind the memory problems, but, "I just felt kind of stupid, really, not being able to give him an answer," Turner recalls. He decided to test his patient for a peptide called amyloid-beta, whose aberrant accumulation is the hallmark of Alzheimer's disease. Turner suggested using positron-emission tomography (PET) scans to check for the protein in the man's brain. The scans confirmed a significant presence of amyloid-beta. "It wasn't just subtle or borderline," Turner says, adding that the significant amount of amyloid meant that the test was "clearly positive" for Alzheimer's disease. Turner published his findings in 2016 and believes that his is the first published report of a person with both HIV and Alzheimer's disease pathology[1].

In 2014, about 27% of the HIV-positive population in the US was aged 55 or older. More of these patients are now entering their sixties, the prime age when Alzheimer's-like symptoms begin to manifest. HIV can prematurely age the brains of those with the disease and lead to neurocognitive decline[2], as can Alzheimer's disease, which itself can worsen cognitive decline in as little as two years from onset. Given the commonalities, scientists are considering the possibility that HIV could create conditions ripe for the development of Alzheimer's. To that end, Turner and others think it's imperative to be able to distinguish symptoms of HAND from those of Alzheimer's disease to identify the problem and decide on the best course of treatment. Currently, clinicians in San Francisco, Baltimore and St. Louis have identified at least 20 patients who have both HIV and Alzheimer's disease, and while there isn't an epidemic of patients with both diseases, these clinicians are clear that a link between the two diseases is worth investigating. "I'm trying to make the case that HAND's not the end of the story," Turner says.

The wider scientific community is also curious about this connection. Last fall several US federal institutes put on a joint conference in Rockville, Maryland to address neurological issues affecting the HIV population. One of the pressing issues discussed at the meeting, according to some



Assessing amyloid: (left to right) An HIV-infected, cognitively-normal individual; HIV individual with HAND; an uninfected, cognitively unimpaired individual; HIV-uninfected individual with Alzheimer's disease. The colors, in the order of a rainbow, show increasing levels of amyloid.

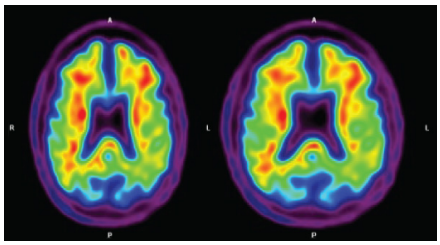
conference attendees, was how to separate HAND from Alzheimer's disease. Separately, in November, the National Institute on Aging announced a $5-million research grant for research projects aimed at better understanding HIV-related neurodegeneration. The funding opportunity especially encourages research into Alzheimer's disease and other related conditions in older adults with HIV. "This is the main issue for patients right now," says Jules Levin, executive director of the National AIDS Treatment Advocacy Project and a 68-year-old living with HIV. "If researchers and doctors don't know what's happening, imagine how patients must feel."

Even if a concrete link cannot be established between HIV and Alzheimer's, researchers think that there are bound to be meaningful takeaways for each disease as both diseases have symptoms of cognitive decline. "This population has never existed before," Turner says. "We really need to study them because we don't know what's going to happen to them."

Coinciding conditions

Beyond HIV, other pathogens, including the herpes simplex virus[3], have been studied as possibly associated with the development of dementia, but the data are still very tenuous. Yet, for more than a decade, scientists have collected data suggesting an association between HIV and the presence in the brain of amyloid-beta, which has been independently implicated in Alzheimer's disease.

In one study of brain samples from 48 people, the five HIV-negative individuals had little or no detectable amyloid protein, but 38% of those with HIV and no dementia had amyloid-beta, as did 72% of those with HIV-associated dementia[4]. The amyloid in the HIV-infected people was mostly within neurons, whereas neuritic plaques in Alzheimer's disease tend to be outside neurons, but researchers don't yet know whether this difference is important. The report's authors suggested that it may be difficult for the brain to clear amyloid in those who survive long term with HIV, possibly because a protein encoded by HIV inhibits the function of an enzyme that is responsible for regular clearing of amyloid.



Giuseppe Esposito

HAND-in-hand: PET scans of Scott Turner's patient with HIV and Alzheimer's disease.

Another hypothesis pins the blame on immune cells, mainly brain macrophages known as microglia, which are known to be HIV reservoirs. Normally, these microglia "eat through all sorts of debris and clear all the junk that accumulates in the brain," explains Cristian Achim, a neurobiologist at the HIV Neurobehavioral Research Center at the University of California, San Diego, but in HIV they might be incapable of clearing amyloid. Achim's team analyzed tissue from the brains of 80 HIV-infected individuals and posited that HIV replication in the brain might activate microglia, which in turn seem to mediate inflammation of brain tissue and improper clearance of proteins, including amyloid-beta[5].

The "triple whammy," Achim speculates, may be that antiretroviral therapy (ART) may contribute to amyloid buildup. A study found that mouse neuronal cells treated with four different ART medications, in combination and alone, experienced a 50%-200% increase in amyloid-beta production when compared with mouse nerve cells in a saline solution[6]. A group of scientists found that these medications, known as protease inhibitors, were associated with an increase in cerebral small vessel disease in a group of HIV-positive adults, which increases the risk of Alzheimer's disease[7].

A possible HIV–Alzheimer's connection is not without its doubters. Beau Ances, a neurologist at Washington University in St. Louis, has conducted PET imaging studies to compare levels of amyloid in HIV-infected and uninfected individuals, with and without cognitive impairment. His group found that the amyloid-beta levels in HIV-positive people, regardless of impairment, was more similar to HIV-negative people who were unimpaired[8]. If, as the thinking goes, aging in HIV infection is accelerated, you would expect to see amyloid levels similar to the HIV-negative and cognitively impaired group, Ances says, adding, "We haven't seen that." In unpublished work, Ances' group also looked at a related Alzheimer's protein, tau, and didn't find similarities between HIV-positive people and HIV-negative people with cognitive impairment. "It may be that amyloid and tau don't work in HIV the way they do in Alzheimer's," Ances says.

Few disagree on the need for concrete answers, however. Victor Valcour, for instance, is developing a diagnostic standard to distinguish between HAND and Alzheimer's disease. Two years ago, his group outlined a machine-learning method to differentiate HAND from Alzheimer's disease using data from magnetic resonance imaging (MRI) scans[9]. PET scans for amyloid still aren't widely available, says Valcour, a neurologist at the University of California, San Francisco's Memory and Aging Center, and so neurologists have to rely on other ways of detecting the problem. Turner is recruiting for a small, observational trial to compare the cognition of those with HIV and a PET scan positive for amyloid-beta against those with only a positive PET scan. Recruitment for the trial is very difficult, he says, because the patients are on average 65 years old and participants need to undergo a spinal tap to get their cerebrospinal fluid for testing. "It could all be coincidence," Turner says of the link between HIV and Alzheimer's, "but we really need to study this to figure out the problem."

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