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Brain cell injury in HIV infection

When does it start and can it be stopped?

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HOW WAS THE STUDY DONE? The study by Young and colleagues[1] in this issue of *Neurology*® used a technique called magnetic resonance spectroscopy (MRS) to examine the brain chemistry of patients with HIV. MRS is a noninvasive method of measuring the levels of certain chemicals, or "metabolites," in the brain. One metabolite, *N*-acetylaspartate (NAA), is a marker of healthy brain cells. Three other metabolites, choline (Cho), myo-inositol (MI), and glutamate (Glu), are markers of damaged brain cells and inflammation (see table).

The researchers used MRS to study these brain metabolites in 53 people who were within 1 year of initial HIV infection. For each person, brain MRS was repeated after 6 weeks and then every 6 months until the end of the study. This allowed the researchers to see the changes in brain metabolites over time. During the study, 23 of the participants started taking antiretroviral therapy (ART), which allowed Young and colleagues to compare the brain metabolites before and after treatment with ART.

WHY IS THIS STUDY IMPORTANT? According to the Centers for Disease Control and Prevention, there are about 1.1 million people in the United States who have been infected with HIV. Almost 50,000 more people are diagnosed each year.[2] When HIV infection is not controlled, it can injure the immune system and cause a condition called AIDS.

HIV can also affect the function of the brain. HIV infection can result in problems with thinking, memory, learning, and communication, as well as changes in personality and behavior. At first, the decline in brain function may be mild and barely noticeable. But in some people, the symptoms become more severe. When the symptoms become severe enough to interfere with daily activities (eating, dressing, bathing, etc.), it is called dementia (see "About HIV" in the following section).

In the mid-1990s, doctors began treating HIV with drugs known as ART. Before this, many people with HIV developed dementia. Due to ART, fewer people develop HIV-associated dementia. However, it is becoming clear that many people receiving ART still have important problems with brain function.

Researchers have determined that over time, HIV infection causes brain cell inflammation and injury. This leads to changes in brain chemistry. However, little is known about these changes early in the course of the disease. How soon after the initial infection do these changes happen? Can they be slowed or stopped with ART? These are questions that the authors of the current study wanted to address.

Table Metabolites measured on magnetic resonance spectroscopy (MRS)

Metabolite	Abbreviation	Significance
N-Acetylaspartate	NAA	Marker of healthy brain cells
Choline	Cho	Damaged brain cells, inflammation
Myo-inositol	MI	Damaged brain cells, inflammation
Glutamate	Glu	Brain cell dysfunction, toxicity

WHAT WERE THE RESULTS? The MRS results showed that levels of Cho, MI, and Glu began to rise within the first year of HIV infection. This shows that the process of brain cell inflammation and injury begins very early after infection.

The researchers also observed something very important in those taking ART. In these people, the levels of Cho and MI stopped increasing, and the levels of Glu actually decreased. These findings suggest that ART is able to slow or may even stop the ongoing brain cell inflammation and injury seen in early HIV infection.

WHAT ARE THE NEXT STEPS? The study suggests that the brain injury caused by HIV infection begins very early in the course of the disease, likely before patients have any symptoms. But it also suggests that ART can slow or even stop brain inflammation and injury that leads to these symptoms.

Most patients in this study who began ART did so about 6 months after HIV transmission. If treatment were started earlier, could it completely prevent the brain cell injury? One study of military members with HIV found a much lower rate of cognitive problems than in the civilian population. This may be due to

required testing and free access to health care, which enabled earlier treatment.[3]

Will longer periods of treatment continue to reduce or eliminate inflammation in the brain? What do the improved levels of brain metabolites mean for the day-to-day brain function of patients with HIV? If ART is started early and continued, can dementia and other cognitive problems be prevented in the long term? MRS may be a valuable tool in future research to answer these questions.

REFERENCES

1. Young AC, Yiannoutsos CT, Hegde M, et al. Cerebral metabolite changes prior to and after antiretroviral therapy in primary HIV infection. Neurology 2014;83:1592–1600.
2. HIV/AIDS statistics overview. Centers for Disease Control and Prevention Web site. Updated December 20, 2013. Available at: http://www.cdc.gov/hiv/statistics/basics. Accessed August 16, 2014.
3. Crum-Cianflone NF, Moore DJ, Letendre S, et al. Low prevalence of neurocognitive impairment in early diagnosed and managed HIV-infected persons. Neurology 2013;80:371–379.

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About HIV

What is it and how does it affect the brain?

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WHAT IS HIV? HIV is a type of virus called a retrovirus that impairs the body's ability to fight infections. The virus attacks and reduces the number of blood cells called T cells. These cells play a central role in the immune system. If the number of T cells drops too low, the immune system becomes very weak. This leads to a high risk for becoming seriously ill from many kinds of infection that might not cause a problem for someone with a healthy immune system. This stage of the infection is called AIDS.

WHO IS AT RISK OF HIV INFECTION? In the United States, HIV is most commonly spread when someone has sexual contact with an infected person or when someone injects drugs with a needle that has been contaminated with the virus. Therefore, people who engage in unsafe sexual practices and those who use IV drugs are at highest risk for HIV infection.

HOW IS HIV INFECTION CURRENTLY TREATED? Antiretroviral therapy (ART) is the main treatment for HIV infection. ART consists of several classes of drugs, which are often taken in combinations to achieve the best results. Currently, there is no cure or vaccine for HIV/AIDS. However, consistent use of ART medications controls the virus and greatly reduces the risk of developing AIDS and its complications.

HOW DOES HIV AFFECT THE BRAIN? One way that HIV infection causes disease in the brain is by weakening the immune system. This increases the chances of an infection involving the brain or meninges (the protective covering of the brain). These are dangerous infections that can lead to seizures, coma, or even death.

Another way that HIV affects the brain is by causing harmful inflammation and injuring brain cells. This inflammation and injury may lead to problems with normal brain function. These problems can range from very mild to very severe. As a whole, these problems are called HIV-associated neurocognitive disorders.

Those with a milder case may not have obvious symptoms. This is called asymptomatic neurocognitive impairment (ANI). People with ANI have normal function but they do not perform as well as healthy people on formal tests of thinking ability. In the middle of the range is a condition called mild neurocognitive disorder (MND). Patients with MND have some neurologic symptoms, such as difficulty finding the right word or problems with organizational skills. They would also have some difficulty with everyday activities. On the severe end of the range, patients with HIV-associated dementia (HAD) may experience language and memory problems, coordination issues, walking difficulties, and personality changes. These hinder the person's ability to function in everyday life.

WHO IS AT RISK FOR DEVELOPING AN HIV-ASSOCIATED NEUROCOGNITIVE DISORDER? Fortunately, the use of ART has reduced the number of people who develop severe dementia (HAD) due to HIV. However, the milder forms of cognitive impairment (ANI and MND) are still common, even in patients who take ART medications. Patients are at higher risk for developing these conditions if they have other coexisting infections, if they use illicit drugs, or if their body is not responding well to ART.

CAN HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS BE PREVENTED? Aside from preventing HIV infection in the first place, there is no proven way of preventing an HIV-associated neurocognitive disorder. Research suggests that early diagnosis and treatment of HIV infection may reduce the risk of neurologic involvement, but more research is needed to determine the specific regimen of ART medications that should be used.

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Centers for Disease Control and Prevention: Act Against AIDS
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National Institute of Neurologic Disorders and Stroke: Neurological Complications of AIDS Information Page
http://www.ninds.nih.gov/disorders/aids/aids.htm

NIH: AIDS Info Home Page
http://www.aidsinfo.nih.gov/

US Department of Health and Human Services: AIDS Information Page
www.AIDS.gov

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Neurology 2014;83;e171-e173
DOI 10.1212/WNL.0000000000001016