Virus responsible for deadly brain disease found in MS patients treated with natalizumab

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The virus responsible for PML (progressive multifocal leukoencephalopathy), a rare brain disease that typically affects AIDS patients and other individuals with compromised immune systems, has been found to be reactivated in multiple-sclerosis patients being treated with natalizumab (Tysabri). The findings, led by scientists at Beth Israel Deaconess Medical Center (BIDMC), appear in tomorrow's issue of The *New England Journal of Medicine* (*NEJM*).

"This virus - the JC virus, named for the initials of a patient- is found in about 90 percent of the population," explains Igor Koralnik, MD, the study's senior author and director of the Human Immunodeficiency Virus/Neurology Center at BIDMC. "But in healthy individuals the virus lies dormant in the kidneys and causes no problems." Urine samples of healthy individuals may, therefore, show evidence of the benign virus.

But, according to Koralnik, who is also Associate Professor of Neurology at Harvard Medical School and a world leader in the study of PML, among AIDS patients and other patients with compromised immune systems, the JC virus can reactivate and travel to the brain, leading to the development of PML, a destructive brain disorder that may cause numerous neurological symptoms, including dementia, blindness, paralysis, and seizures. There is no cure for PML and more than half of all PML patients die within a year of diagnosis.

Four years ago, PML was diagnosed in two patients who were participating in a clinical trial testing natalizumab, a new drug for the treatment of multiple sclerosis (MS). An autoimmune disease caused by the migration of the immune system's T lymphocytes to the brain, MS results in relapsing and remitting neurologic dysfunction when the T lymphocytes attack the myelin, the insulating sheath that covers the nerves.

"This was the first time we had seen PML develop in patients with multiple sclerosis," notes Koralnik. Because natalizumab, or Tysabri, prevents lymphocytes from crossing the blood-vessel wall, some doctors theorized that it was also providing an opportunity for the dormant PML virus to take hold. "The drug appeared to be something of a double-edged sword," notes Koralnik. "Not only was it keeping dangerous cells from entering the brain, it was also keeping out the protective virus-fighting lymphocytes, thereby leaving patients vulnerable to this dangerous infection.

"If impaired immune surveillance due to natalizumab treatment was responsible for the development of PML, we wanted to find out where in the body the JC virus reactivation was taking place," he adds, explaining that the scientists also wanted to determine whether the reactivated JC virus had the benign molecular composition commonly found in the urine of healthy individuals - or if it had acquired changes typically found only in the brains of patients with PML.

To answer these questions, the scientists enrolled 19 multiple sclerosis patients for a clinical study as they began treatment with natalizumab. They then followed them at intervals of three, six, 12 and 18 months, post-treatment.

Their results showed that measurements of the JC virus in patients' urine increased from 19 percent (before beginning treatment) to 63 percent

after 12 months of using natalizumab. Six months later - 18 months after beginning treatment - blood samples further revealed that the virus had additionally entered the blood cells of 60 percent of these patients. (At 12 months of treatment, only one patient had the virus in their blood.)

"These JC virus measures were higher than viral measures found in patients infected with the HIV virus, and similar to measures seen in patients with full-blown PML," explains Koralnik.

The researchers then proceeded to evaluate patients' immune responses against the JC virus, since these immune blood cells play a crucial role in the containment of PML.

"What we saw surprised us," he adds. "Between six and 12 months after beginning the natalizumab treatment, there was a significant drop in the magnitude of patients' immune responses against the virus. Since natalizumab was only supposed to prevent migration of lymphocytes out of the bloodstream - but not directly alter their potency - this finding was quite unexpected."

Finally, he adds, the scientists made another startling discovery: Further analysis showed that among many of the MS patients using natalizumab, the JC virus that was detected in their urine or blood samples had already acquired the signature changes associated with the virus's ability to reach the brain and cause PML.

"This pilot study shows for the first time that natalizumab not only prevents the migration of protective T lymphocytes, but it also directly affects the cells' potency against the JC virus," says Koralnik. "It further tells us that reactivation and transformation of the virus may first occur in the kidney and that once the activated virus spills into the blood it can easily spread to the brain."

Because none of the 19 patients tested developed any symptoms or brain lesions suggestive of PML during the course of the study, the authors do not suggest any change in the management of multiple sclerosis.

"As of July 24, 2009, there was a worldwide total of 13 natalizumab-treated MS patients who had developed PML," he adds. "We hope that the results of our study will stimulate further research, and that monitoring the appearance of the virus in the blood and urine may allow for early identification of natalizumab-treated patients at risk of developing PML."

Source: Beth Israel Deaconess Medical Center