Discovery could lead to faster diagnosis for some chronic fatigue syndrome cases

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For the first time, researchers have landed on a potential diagnostic method to identify at least a subset of patients with chronic fatigue syndrome (CFS), a complex disorder with no known definitive cause or cure.

In a pilot study of six patients, scientists detected specific antibodies linked to latent Epstein-Barr virus reactivation in blood samples from people who had experienced classic CFS symptoms and responded to antiviral treatment. Control blood samples from 20 healthy people showed no such antibodies.

The research team, led by scientists from Ohio State University and Oakland University William Beaumont School of Medicine, acknowledges that the number of patients is small. But the researchers say the study's power rests in their access to 16 months of blood samples for each patient – a collection allowing for an unprecedented longitudinal look at CFS.

The researchers plan to move forward with development of a clinical laboratory test that can detect these antibodies in blood samples.

The study is published in the Nov. 14 issue of the journal PLOS ONE.

The Epstein-Barr virus is a human herpes virus that causes infectious mononucleosis and several different types of tumors. An estimated 95 percent of Americans have been infected with the virus by adulthood,

according to the Centers for Disease Control and Prevention (CDC), but fewer than half have experienced an active illness. Once a person is infected, the virus remains dormant in the body, and can be reactivated without causing symptoms of illness.

In these six patients, the study suggests that a latent Epstein-Barr virus had begun to reactivate, but that the newly awakened virus never reached its full potential to take over its host cells. That partial reactivation advanced enough to generate at least two viral proteins, DNA polymerase and dUTPase, and these patients produced antibodies specifically designed to identify and neutralize those proteins for more than a year.

The scientists theorize that even in the absence of a complete active infection, these viral proteins' ability to induce inflammatory chemical signals causes enough immune system chaos to lead to CFS. The disorder's main symptom is profound fatigue for at least six months that does not improve with rest, and is accompanied by problems that can include weakness, muscle pain, impaired memory and depression. Because the illness mimics many other disorders, diagnosis is difficult. An estimated 1 million Americans have CFS, but experts believe only 20 percent are diagnosed.

The study's senior researchers agree that the work should be repeated in more patients "to confirm that these observations are real," said virologist Ron Glaser, director of the Institute for Behavioral Medicine Research at Ohio State and a co-author of the study. "But finally, after more than 20 years, this is at least something to go on."

Glaser's primary collaborators on this work are Marshall Williams, professor of molecular virology, immunology and medical genetics at Ohio State, and A. Martin Lerner, a professor of internal medicine at Oakland University William Beaumont School of Medicine.

Ohio State and Lerner's private practice, CFS LLC, have applied for a patent for the diagnostic method.

Glaser and Williams first published a paper in 1988 suggesting that these two viral proteins associated with partially reactivated Epstein-Barr virus could function as biomarkers for certain illnesses, including CFS. Meanwhile, Lerner became severely ill in 1986 and struggled for 10 years with CFS symptoms before treatment with antivirals dramatically improved his health.

Lerner, an infectious diseases specialist, runs his private CFS practice in Michigan, and his long-term tracking of patients' characteristics and response to treatment made this longitudinal research possible.

The fact that CFS patients experience different symptoms and multiple types of viral and bacterial infections has led researchers to believe CFS potentially has numerous causes. That lack of uniformity also complicates the diagnostic process and development of treatments.

"Part of the problem in trying to identify an agent or biomarkers for chronic fatigue syndrome is the extreme variability among people who say they have CFS. How to sort that out has held the field back a lot of years," said Glaser, who has studied the Epstein-Barr virus (EBV) for decades.

Lerner had long ago separated 142 of his patients into two groups: those who had tested positive for various antibodies against three types of herpes viruses and responded to months-long treatment with one of two types of antivirals, and a smaller group that had viral infections and a variety of co-infections who showed minimal response to antiviral treatment. As part of this tracking, he collected multiple blood serum samples for more than a year from each patient.

From those patients, he selected blood samples from six for this study. Five had been identified as an Epstein-Barr virus subset, and the sixth had Epstein-Barr virus and a bacterial co-infection. For comparison, researchers collected samples from 20 healthy people matched to the six CFS patients for age and sex.

Lerner, too, had independently hypothesized that CFS patients might be experiencing partial virus reactivation. Patients might test negative for the most active antibodies required to fight a virus, but could still recover from CFS after long-term antiviral treatment. One antiviral he uses is known to inhibit DNA polymerase, which would halt Epstein-Barr virus reactivation in its tracks.

With the CFS patients' and control blood samples in hand, Williams used a highly sensitive laboratory method to detect whether they contained antibodies to the two target Epstein-Barr viral proteins, DNA polymerase and dUTPase, that are produced early in the process of viral reactivation.

Overall, 78.8 percent of the serum samples from the six CFS patients were positive for antibodies against DNA polymerase and 44.2 percent were positive for antibodies against dUTPase. No antibodies to these two proteins were detected in the 20 control samples.

"Every one of the six had antibodies to DNA polymerase or EBV dUTPase and those antibodies persisted over some 408 days," Lerner said. "And the antibody levels were extraordinarily high." High levels of antibodies circulating in the blood suggest long-term immune activation against those proteins.

Williams noted that the levels might be less significant than the antibodies being present in the first place.

"If you look at most healthy individuals, they wouldn't have any reason

to have an antibody against either of these proteins," he said. "The antibodies alone are a good differentiator."

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