Harmful effects of long-term alcohol use documented in blood protein snapshot

February 9 2023

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Biochemist Jon Jacobs has analyzed the blood of patients with diseases and conditions such as Ebola, cancer, tuberculosis, hepatitis, diabetes, Lyme disease, brain injury and influenza.

But never has he seen blood chemistry gone so awry as when he and colleagues took an in-depth look at the protein activity in the blood of patients with alcohol-associated hepatitis, a severe form of liver disease caused by heavy drinking for many years.

"The proteins in these patients are more dysregulated than in any other blood plasma that we've analyzed," said Jacobs, a biochemist at the Department of Energy's Pacific Northwest National Laboratory. "Almost two-thirds of the proteins we measured are at unusual levels. This is a snapshot of what's going on in the body of a person with this disease and reflects just how severe a disease this is."

That "snapshot" is a measurement of proteins that change in patients with the disease. The unique combination of changes in protein activity marks an important step toward development of a simple blood test to diagnose alcohol-associated hepatitis.

Jacobs and colleagues, including scientists and physicians from the Veteran Affairs Long Beach Healthcare System and the University of Pittsburgh, have published their findings in the *American Journal of Pathology*. Corresponding authors of the study are Jacobs and Timothy Morgan, a gastroenterologist at VA Long Beach who has treated patients with the disease for more than 35 years.

Alcohol-associated hepatitis: Long in the making

The findings don't surprise Morgan.

"These individuals are very sick. These patients have been drinking a lot of alcohol, typically more than a six-pack of beer or more than a bottle of wine or more than four shots of liquor per day for more than 10 years," said Morgan, who is also professor of medicine at UCI Health.

The disease is more severe than other liver diseases that can be caused by alcohol, including liver cirrhosis and fatty liver. About 10 percent of patients with alcohol-associated hepatitis die within one month of diagnosis; about 25 percent die within six months. They're often in the last throes of an illness that has been in the making for many years.

Morgan estimates that he has treated more than 400 patients with the disease. To improve the care he provides to patients and to learn more about the disease, Morgan brought together researchers, physicians, and patients from the Southern California Alcoholic Hepatitis Consortium, PNNL, the InTeam Consortium based at the University of Pittsburgh, and others.

The study included analysis of blood or tissue samples from 106 people. These included 57 patients with alcohol-associated hepatitis and 49 others who either had nonalcoholic fatty liver disease, other alcohol-related liver diseases like cirrhosis, or who were healthy.

The PNNL team used sensitive mass spectrometry to measure more than 1,500 proteins in the blood of the study participants. Though alcohol-associated hepatitis has an overwhelming impact on proteins in the blood, the PNNL team identified a group of 100 proteins that are altered in patients and seem to drive the specific disease. Many proteins were less plentiful in those patients; some were more abundant. The affected proteins cover the gamut of bodily functions, including inflammation, immunity and clotting, as well as fundamental liver function.

The results correlated well with previous alcohol-associated hepatitis studies involving patient liver tissues. Ramon Bataller, chief of hepatology at the University of Pittsburgh and an author of the current study, had previously characterized gene activity in the livers of patients with the disease. His team found that the core proteins altered in the disease patients' blood directly correlate with the vast dysregulation of

the genes and proteins in the liver, linking disease-specific protein blood expression to liver function.

Both studies point to a central role for a molecule known as HNF4A, which is a central hub of liver gene activity. HNF4A is also involved in diseases like pancreatic cancer and diabetes.

One goal: A biomarker for diagnosis, monitoring

The work is an important step toward developing a blood-based biomarker—a blood test—that would show that someone has alcohol-associated hepatitis.

"The diagnosis of alcohol-associated hepatitis can be difficult, costly, and sometimes can take several days," Morgan said. "Having a blood test for the diagnosis of AH would help physicians make the diagnosis quickly, safely, more accurately, and less expensively than with a liver biopsy."

The team is conducting further studies to see if the same protein changes could be used to monitor how patients are responding to treatment. Doctors typically use steroids to reduce inflammation, but the treatment leaves patients vulnerable to infection.

"These data help us understand what's happening in these patients, and we're hopeful it gives us an additional tool to monitor how patients are responding to treatments," Jacobs said.

In addition to Jacobs, PNNL authors include Marina Gritsenko, Richard D. Smith, and Le Z. Day, as well as former PNNL scientist Komal Kedia, now with Merck. First author of the study is Josepmaría Argemí of the University of Pittsburgh and the Universidad de Navarra.

More information: Josepmaria Argemi et al, Integrated Transcriptomic and Proteomic Analysis Identifies Plasma Biomarkers of Hepatocellular Failure in Alcohol-Associated Hepatitis, *The American Journal of Pathology* (2022). DOI: 10.1016/j.ajpath.2022.08.009