Medical Xpress

Gene test spots those vulnerable to rare but severe side effect of drugs for MS, other conditions

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A large number of drugs used to treat everything from multiple sclerosis to blood cancers to rheumatoid arthritis may cause a rare but often-fatal condition called progressive multifocal leukoencephalopathy (PML).

But a simple genetic test can determine who has a 10-fold higher risk for developing this condition, which means those patients could discuss safer treatment options with their doctors, according to new research.

Researchers said this is the largest study to date on drugs that increase the risk for PML and the genetic link to the disease.

"The increased risk of drug-induced PML in patients testing positive is higher than already-known genetic associations that are used to guide treatments, like BRCA1/2 for breast cancer, yet many neurologists and oncologists may have limited awareness of how many drugs have been linked to PML," said lead study author Peggy Eis, chief technology officer at Population Bio, Inc., in New York City.

"There are no treatments to cure PML, so prevention is the best defense, including knowing your genetic risk," Eis added in an American Neurological Association news release.

PML is a neurological disorder marked by destruction of cells that produce myelin, an oily substance that helps protect nerve cells in the brain, according to the National Organization for Rare Disorders. It is caused by a virus found in up to 85% of the adult population. The virus causes disease only when the immune system is severely weakened, the organization said.

Eis said that even though the chance of developing PML is very low for some of these drugs, patients should still be screened.

"Clearly, warning labels on some of these drugs need to be updated and

can now include a requirement for genetic testing before these drugs are prescribed," Eis said.

A growing number of PML cases have been reported in patients being treated for multiple sclerosis (MS), Crohn's disease, psoriasis, lupus, blood cancers and organ transplants, according to the study.

In all, researchers identified 99 drugs that may pose an issue. People who have one of four recently identified genetic variants are at 10 times the risk of developing PML if they take these drugs, according to the report.

In addition to genetic testing before being given these drugs, Eis said those now taking the medications should be tested.

For the study, the researchers analyzed data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS).

They linked 81 drugs to PML plus 18 more not reported to FAERS but in the same drug class.

Most of the medications are immunosuppressant disease-modifying therapies. The authors looked to see if the drug label listed PML risk and, if so, whether it was listed as a serious adverse event (SAE) or carried a "boxed warning," the FDA's strongest caution.

The largest number of PML cases have been associated with the medication natalizumab, taken for MS, and rituximab, taken during cancer treatment and for rheumatoid arthritis. Both have a boxed warning.

The investigators also found that labels on two common blood cancer drugs, daratumumab and venetoclax, had no warning of the risk of developing PML.

Variants in four genes (C8B, FCN2, LY9, STXBP2) increase by 10 times a person's risk of developing PML when taking one of these drugs.

All four of these genetic variants play a key role in immune pathways and disorders related to activating the JC virus. This virus lies dormant in most people.

After that virus is activated in an immune-compromised person, it can infect the brain and cause PML.

People who are considering taking one of those drugs can learn if they have one of the genetic variants and consider alternative treatments.

Surveys have found patients overwhelmingly want to be tested once they know a genetic test is available, Eis said.

Alternative treatments not associated with PML include interferon-based therapy, glatiramer acetate or teriflunomide in MS patients.

Some patients may also choose to stay on the PML-linked therapies because of their effectiveness, even if they test positive, but their doctors can monitor them more closely for PML. This could include more frequent brain MRIs.

The test for the four genetic variants associated with PML is now available for free in the United States. It can be taken at home and shipped to the lab for analysis.

The study findings were presented on Monday at a meeting of the American Neurological Association held in Philadelphia. Findings presented at medical meetings should be considered preliminary until published in a peer-reviewed journal.

More information: The U.S. National Institute of Neurological Disorders and Stroke has more on PML.

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