Blood Test Shows Promise for Detecting Genetic Changes in Brain Tumors

This minimally invasive approach may reduce the burden on children with diffuse midline glioma.

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A new study has found that a blood test, called a liquid biopsy, may reveal whether a child with a type of brain tumor known as a diffuse midline glioma has a specific genetic mutation associated with the disease.

The finding that DNA from these tumors can be detected in blood means that it should be possible to identify and follow molecular changes in children with these rare and highly lethal brain tumors using a minimally invasive test, according to the study's leaders. The study was published in Clinical Cancer Research on October 15, 2018.

"Now that we know it's possible to detect a genetic mutation associated with brain tumors in a noninvasive way, we think this approach could change how we follow patients in the clinic in the future," said coauthor Sabine Mueller, MD, PhD, of the University of California, San Francisco Benioff Children's Hospitals and Children's National Health System.

For example, doctors might be able to use information from liquid biopsies to identify signs of a recurrence of brain cancer earlier than is possible with current approaches, such as MRI scans, Mueller continued.

The ability to detect genetic alterations in pediatric brain tumors at diagnosis and as the disease progresses is also critical "for understanding the disease and for developing much-needed new treatments," Mueller said.

The test—which was developed by coauthor Javad Nazarian, PhD, also of Children's National Health System and George Washington University School of Medicine and Health Sciences, and his colleagues—is still being investigated and is not ready for clinical use, according to the researchers.

Detecting a Common Mutation in a Rare Brain Tumor

Liquid biopsies have been developed for adults with cancer, but this study was among the first to

evaluate the approach in children with cancer.

The researchers used a technique called droplet digital polymerase chain reaction to see if they could detect a specific genetic mutation in the blood and in cerebrospinal fluid collected from spinal punctures.

The researchers focused on a genetic mutation called K27M, which occurs in the H3 gene and is associated with an aggressive form of the disease. The test identified the mutation in the blood or cerebrospinal fluid (or both) of 42 of the 48 patients with diffuse midline gliomas in the study known to carry the mutation.

Previous studies have shown that more than 70% of patients with diffuse midline gliomas have this mutation in the H3 gene, which encodes a histone protein. This mutation has been a focus of researchers' efforts to better understand the disease and explore potential treatments.

There currently are no effective treatments for these rare brain tumors, and median survival for patients is less than a year.

By comparing the MRI scans and liquid biopsy results of 12 patients with one type of diffuse midline glioma, called diffuse intrinsic pontine glioma (DIPG), before and after they received radiation therapy, the researchers found that the liquid biopsy results corresponded to changes in brain tumors.

Specifically, the blood levels of tumor DNA fell when patients responded to therapy and rose when the disease progressed, noted Nazarian.

Although the H3 gene mutation could be detected in the cerebrospinal fluid as well as blood, Mueller noted that a spinal tap is more invasive and that sometimes it's not safe to perform the procedure in these children.

Other Potential Applications for Liquid Biopsies in Children with Brain Tumors

In adults with cancer, liquid biopsies have been used to monitor the development of cancer, track a patient's response to treatment, and monitor patients who have completed treatment but are at risk of the disease returning.

For children with brain tumors, liquid biopsies could be used in various ways, including to monitor patients who have undergone a surgical biopsy and whose tumors have been evaluated for certain genetic changes.

"These cancers recur," said Nazarian. "If a patient's cancer is treated and we know the tumor profile from a surgical biopsy, then that patient would be an ideal candidate to be monitored over time."

Doctors could potentially check a patient's blood every month, Nazarian explained.

His team is working to improve the accuracy of the test, which detects the mutation in an estimated 85% of the patients whose tumors carry it. The researchers also expect to add additional genetic mutations involved in the disease to the test as they are discovered.

Liquid biopsies could also be used to profile the brain tumors of patients who are not candidates for surgical biopsy, the researchers noted.

Several clinical trials are enrolling patients with brain tumors that harbor the H3 mutation, including a study testing immunotherapy in patients with DIPG or any glioma that has the mutation.

“If a patient is not a candidate for a surgical biopsy then he or she can’t enroll on a trial that requires patients to have a certain mutation,” said study coauthor Katherine E. Warren, MD, of the Pediatric Oncology Branch in NCI’s Center for Cancer Research.

“Once we collect more patients and validate this process, I think liquid biopsy could be used to detect certain genetic mutations associated with brain tumors in patients who cannot undergo surgical biopsy,” she added.

Providing Another Perspective on Brain Tumors

In addition to helping patients enroll on the appropriate clinical trials, liquid biopsies could also give investigators information about tumors that is not currently available through other methods, such as MRI scans.

“The hope is to use circulating tumor DNA to learn whether a tumor has progressed, especially now that we are starting to treat some of these patients with immunotherapy,” said Mueller.

With MRI, it is not always clear what is happening with a tumor, she continued. MRI scans may suggest that a tumor is progressing when, in fact, the tumor changes are actually a reflection of the body’s response to the tumor, a phenomenon known as pseudo-progression.

“The tumor looks bigger on MRI, but we don’t know if that’s because the tumor is progressing or because of the body’s immune response to the tumor,” Mueller explained. A liquid biopsy may help answer this question, she added.

Indeed, Warren noted that, until recently, liquid biopsies for childhood cancers seemed like a “futuristic” technology. But she pointed out that new approaches and treatments are needed for pediatric brain tumors.

“If we could use this minimally invasive approach to reduce the burden on these patients and their families, that would be incredibly important,” Warren added. “Because these patients go through so much.”

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