Researchers reverse severe lymphatic disorder in patient with Noonan syndrome

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Researchers at Children's Hospital of Philadelphia (CHOP) have resolved a severe lymphatic disorder in a girl with Noonan Syndrome that had led to upper gastrointestinal bleeding, fluid collection around

the lungs, and numerous surgeries that had been unable to resolve her symptoms. By identifying a genetic mutation along a pathway related to lymphatic vessel development and function, the research team was able to target the pathway using an existing drug they had used in a previous case to remodel a patient's lymphatic system.

The case study, which was published today in *Pediatrics,* describes a resolution of the patient's symptoms within three months while on the medication.

"This study is quite significant," said first author Yoav Dori, MD, Ph.D., Director of the Jill and Mark Fishman Center for Lymphatic Disorders at CHOP. "Inhibiting this pathway seems to have sweeping, widespread effects on the lymphatic system. How this process occurs is not fully understood, but is remarkable in its speed and breadth. This gives us a lot of hope for treating other patients with genetic mutations along this same pathway in the future."

The patient described in the paper, Maria, first came to CHOP when she was 14, after experiencing severe anemia due to upper gastrointestinal bleeding, as well as other symptoms including fluid build-up in the cavity around her lungs, chronic fatigue, delayed puberty, and difficulty gaining weight. Maria had been born with Noonan Syndrome, a genetic disorder that prevents normal development in various parts of the body and often results in short stature, heart defects and other physical problems, including an abnormal lymphatic system. Despite aggressive medical therapy elsewhere, Maria continued to bleed internally, and she underwent multiple blood transfusions to try to stabilize her health.

Within two days of transferring to CHOP, the lymphatics team, led by Dori, determined Maria had many lymphatic irregularities, which were leading to internal bleeding and lung problems, so they scheduled Maria's first intervention, a lymphatic embolization procedure that

would seal the leaky vessels in her gut.

However, within two months of the procedure, Maria's gastrointestinal bleeding recurred. Over the following 8 months, she underwent two additional procedures, as well as a cauterization procedure to close off some of the blood vessels in her gut, but the benefits of each procedure lasted only about three months before the bleeding and her symptoms returned.

Based on whole exome sequencing done at CHOP's Center for Applied Genomics, the research team learned that Maria had a genetic mutation in the SOS1 gene, which operates along the RAS-MAPK pathway. This pathway involves mitogen-activated protein kinase (MEK), and Maria's mutation caused an overproduction of MEK, which resulted in the uncontrolled proliferation of her lymphatic vessels.

The research team had previously used a MEK inhibitor in another patient with a severe lymphatic disorder with great success. That patient had a mutation in the ARAF gene, which is also on the RAS-MAPK pathway. Within months of beginning treatment with trametinib, a MEK inhibitor, the patient saw a resolution of his symptoms and a complete remodeling of his lymphatic system.

Given that SOS1 operates on the same pathway as ARAF, Jean Belasco, MD, an oncologist in CHOP's Cancer Center who co-led the study, applied for compassionate use of the drug in Maria's case, given the lack of other treatment options.

"The success of trametinib in another patient with a mutation on the RAS-MAPK pathway encouraged us to try this approach, since other procedures and therapies continued to be unsuccessful," Belasco said. "Although we are in the early days of this type of personalized medicine, the hope is that by looking at patients' mutations, we can find more drugs

and better care for patients with genetic diseases."

Within three months of starting the drug, Maria's vital signs stabilized. The bleeding stopped, her electrolyte, hemoglobin, and albumin levels returned to normal, and she began to gain weight. Maria's mother noticed that Maria wasn't going through periods of exhaustion anymore, and her pallor improved.

"She looks better than she's ever looked," her mother said. "She looks like a normal teenager. It's like night and day. She's also a lot happier. I think she knew deep down she was dying. The medicine gave her hope."

Hakon Hakonarson, Director of the Center for Applied Genomics and co-author of the paper, said that although Maria's SOS1 mutation is distinctly different than the ARAF mutation seen in the other patient, the drug was equally effective because it targets and blocks the function of MEK. He likened the scenario to a pathway where 15 events need to occur for a cell to function. Maria's SOS1 mutation might occur at step nine, whereas the ARAF mutation might occur at step three, but both genes are on a chain that ultimately passes through a tunnel that leads to phosphorylation and overactivity of MEK. Since both mutations were so-called gain of function mutations, MEK—and thus lymphatic activity—was overexpressed in both patients. The MEK inhibitor put the brakes on a system in overdrive.

"Remarkable advances in genetics have allowed us to uncover these mutations and cluster them into selective pathways and determine effective therapies based on genetic mutations with very high precision," said Hakonarson. "No one could have guessed that this drug would have worked for Maria without knowing the underlying genetics. This discovery is extremely important because Noonan Syndrome has the biggest patient population with alterations in MEK signaling. Not all Noonan patients will have mutations that respond to this therapy, but a

very good number of them will."

He added that the treatment could also benefit patients with other genetic defects, though he noted the ongoing use of the drug treats the symptoms caused by these mutations, but does not fix the gene or cure the underlying condition.

"MEK inhibition has the potential to have significant effects on other organ systems affected by RAS-MAPK gene defects, such as the heart, eyes, skin and the coagulation system," Hakonarson said.

Hakonarson is also part of CHOP's Comprehensive Vascular Anomalies Program (CVAP), a CHOP Frontier Program that uses state-of-the-art genomics and personalized research strategies to determine the causes of complex vascular conditions and identify targeted therapies. The program works closely with the Lymphatic Imaging and Interventions Frontier Program, which is led by Dori. CHOP's Frontier Programs conduct cutting-edge research that translates into advanced clinical care. The CVAP, in particular, draws on the extensive clinical and genomic research capacity within the Cancer Center and Center for Applied Genomics.

Even with the success of the breakthrough treatment pioneered by these programs, it is not entirely clear why MEK inhibitors not only resolve patients' symptoms but also completely remodel their lymphatic systems. Hakonarson said one possibility is that when mutated genes cause uncontrolled growth of the lymphatic system, the body's vessels leak fluid everywhere in the body. When you shut down the unregulated growth, other homeostatic mechanisms that are balancing the system come into effect, so the overreactive cells that were growing out of control die and are replaced by normal cells that gradually build up the lymphatic system.

Whatever the mechanism, Maria's mother said her daughter had no hesitation at being the first patient with Noonan Syndrome to try this treatment to resolve a lymphatic issue.

"Maria saw the value from the beginning," she said. "She saw the value for herself, but she was also thinking of other Noonan kids, some of whom have passed away from lymphatic issues. She was willing and eager."

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