Stem cell transplants in utero offers Tx for metabolic disorders that often end pregnancy

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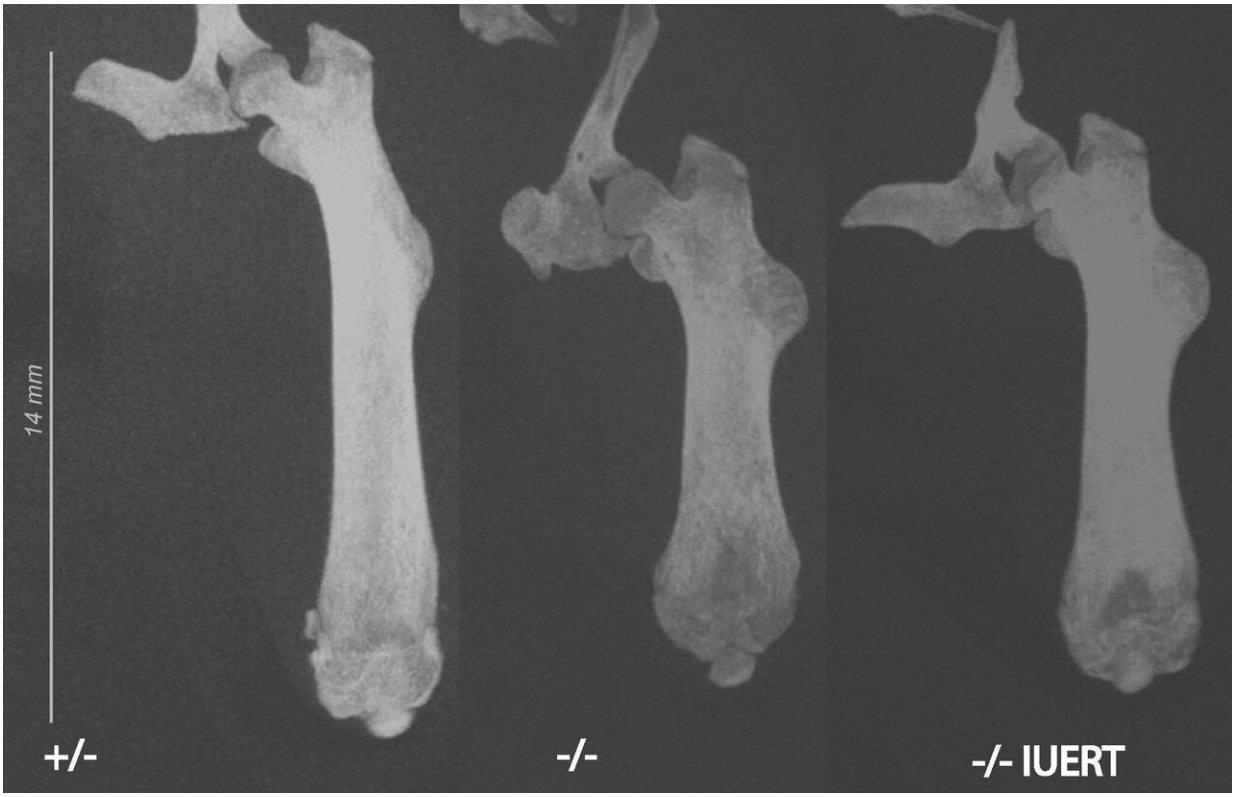

Enzyme replacement therapy both before and after birth (right) partly corrected short femur length in mice with MPS7 (middle), compared with femurs from unaffected mice (left). Credit: Q.-H. Nguyen et al., Science Translational Medicine (2020)

Administering stem cell or enzyme therapy in utero may be a path to

alleviating some congenital diseases that often result in losing a pregnancy, according to a new study in mice by UC San Francisco researchers, who showed that stem cells can enter the fetal brain during prenatal development and make up for cells that fail to make an essential protein.

Each year, about 24,000 women in the US lose a pregnancy. One of the major contributors to this problem is a group of congenital diseases that can cause a condition called hydrops, in which fluid accumulates in the fetus, often to a fatal extent.

"This group of vulnerable patients has been relatively ignored in the fetal surgery world," said UCSF's Tippi MacKenzie, MD, senior author of the new study who has worked for a decade developing novel therapies for heritable diseases that can be treated before birth. "We know these patients could potentially benefit from a number of medical therapies. So this is our first foray into treating one of those diseases."

The new study was aimed at exploring treatments for MPS7, also known as Sly syndrome, a disorder caused by a mutation in a single gene. In this disease the body's cells lack an enzyme to properly process large chains of sugar molecules that are necessary for proper cell function. Sly syndrome is part of a family of related metabolic disorders that can potentially be treated before birth using similar approaches.

The incidence of MPS7 is difficult to determine, because it is believed that many fetuses with the disorder die before birth. Those that survive are treated with regular injections of the enzyme that their cells do not produce on their own.

While these injections can provide some benefit, the enzyme cannot enter the brain through the bloodstream after birth. In some related metabolic diseases, clinicians need to infuse the enzyme directly into the

brain to treat neurological aspects. But because the so-called blood-brain barrier—which protects the brain from potentially damaging substances in the blood—is not fully developed before birth, MacKenzie believed the enzyme would successfully enter the brain at this stage.

Another problem with repeated enzyme infusions for metabolic disorders is that patients can develop an immune response to the enzyme, which their bodies view as "foreign." Infusing the protein before birth could prevent this immune response, since the fetal immune system tends to view new proteins as "friendly," without rejecting them.

MacKenzie, who co-directs UCSF's Center for Maternal-Fetal Precision Medicine, is among the first to attempt enzyme replacement of any sort at the fetal stage. Led by co-first author Russell Witt, MD, these experiments proved to be successful, and the researchers discovered that in utero treatment with the enzyme dramatically improved the survival of the mice to birth.

The researchers continued to give the enzyme after birth, which ultimately resulted in immune tolerance of the enzyme and improvements in multiple organs, including the brain and liver. Moreover, in comprehensive testing of the mice conducted in collaboration with the UCSF lab of Saul Villeda, Ph.D., the researchers noted significantly improved strength in the grip of MPS7 mice—which is generally weak—and in some cases their grip strength approached that of normal mice.

All told, the research team found that in utero enzyme replacement conferred three major improvements, MacKenzie said. "It will enter the brain, the mice develop immune tolerance for it, and the treatment helps sustain the fetus through birth."

These combined advantages, she said, overcome the main limitations of

the current approach of delivering enzyme treatment after birth—but not all of them. Even if the treatment were successfully delivered in the womb, challenges would still arise. Because the enzyme only lasts about two weeks in the body, patients would still require regular injections after birth. And at that point, the blood-brain barrier is fully developed, so the enzyme can't cross into the brain.

Ultimately, MacKenzie said, the answer may lie in giving fetuses stem cells, which could differentiate into new cells—in both the brain and the rest of the body—that could produce the enzyme that the faulty ones don't.

To explore this possibility, MacKenzie worked with research fellow and surgery resident Quoc-Hung Nguyen, MD, to transplant blood-forming stem cells from normally developing mice into fetal mice carrying a genetic mutation that causes MPS7. The researchers were most interested to see whether these cells could reach the brain, and whether they would change into cells called microglia, immune cells that originate from blood-forming stem cells. In a normally developing fetus, once matured, microglia produce and store the necessary enzyme, as well as regulate the immune environment of the brain.

Others have tried transplanting these stem cells, but usually after birth, said Nguyen, and it has been challenging to obtain fully functioning microglia. "We wanted to test this transplant before birth, using the environment of the fetal brain where, in a normal fetus, the stem cells are migrating into the brain to become microglia," he said. "One of our big findings is that these cells truly do become microglia, so there's a huge advantage to transplanting them before birth."

Nguyen tagged the transplanted cells with a fluorescent marker so he could easily identify them and verify that they had successfully crossed the blood-brain barrier and migrated into the brain. To confirm that the

transplanted cells were acting as functional microglia, Nyugen sequenced the RNA that the cells were producing and saw that it matched the proper signature of protein production by microglia.

He also confirmed that the stem cells had also made their way to the liver, kidney, and other organs, and that they became the appropriate cell type needed to produce the needed enzyme in those organs.

The researchers saw that once the stem cells had engrafted in the brain and body and differentiated, they were able to deliver the enzyme to nearby cells and restore their function, a process called cross-correction. The transplanted cells thus fended off the liver disease and other complications associated with MPS7 for the lifespan of the animals.

"We found that even if you have only one or two percent healthy cells circulating, you can drastically improve, for example, liver disease," said MacKenzie. "One good cell can, in effect, correct multiple other cells."

Another advantage of the proposed treatments is that, in humans, they would be performed using the same techniques now used for fetal blood transfusions, which have been performed for decades in hospitals all around the country. "That means that if we do get to a stage of performing fetal therapy for these diseases in humans, the treatments could someday be offered at multiple centers around the world, and the family doesn't necessarily have to travel a long distance to get the care they need," said MacKenzie.

There are a large number of other heritable metabolic disorders that arise from similar faulty single genes, and Nyugen and MacKenzie agree that their approach may be a useful one for these conditions as well.

"These exciting findings are just the tip of the iceberg," said Nyugen. "They open up a whole new approach to treating a range of diseases. At

the same time, there's also a lot of work to do to optimize the treatment for humans."

To that end, MacKenzie is applying to the U.S. Food and Drug Administration to launch a clinical trial of enzyme replacement therapy that will ultimately enroll 10 patients with MPS7 and related metabolic disorders. She already has a similar trial underway, transplanting mothers' stem cells into developing fetuses to treat a blood disorder called alpha thalassemia. With the proposed trial of enzyme replacement therapy, she hopes to expand the scope of fetal molecular therapies to treat metabolic disorders as well as blood disorders in humans.

MacKenzie points out that while fetal molecular therapies are not yet common, the environment and resources at UCSF allow her team to broaden the field, even as it is developing. "With this work, we're pushing the frontiers of fetal surgery into newer, less invasive therapies. At the same time, colleagues at UCSF are performing genetic sequencing of fetuses with hydrops, so that one day we can identify and treat these genetic conditions before birth," she said. "It's exactly this sort of clinical and research environment that can accelerate moving a therapy like this one into humans."

More information: Q.-H. Nguyen el al., "Tolerance induction and microglial engraftment after fetal therapy without conditioning in mice with Mucopolysaccharidosis type VII," *Science Translational Medicine* (2020). stm.sciencemag.org/lookup/doi/ … scitranslmed.aay8980

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