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Human stem cells show promise against fatal children's diseases

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Scientists have used human stem cells to dramatically improve the condition of mice with a neurological condition similar to a set of diseases in children that are invariably fatal, according to an article in the June issue of the journal Cell Stem Cell.

With a one-time injection of stem cells just after birth, scientists were able to repair defective wiring throughout the brain and spinal cord – the entire central nervous system – of mutant "shiverer mice," so called because of the way they shake and wobble. The work marks an important step toward the day when stem cells become an option for the treatment of neurological diseases in people.

Neuroscientists at the University of Rochester Medical Center injected a type of fetal human stem cell known as glial stem cells into newborn mice born with a condition that normally claims their lives within about 20 weeks of birth, after a lifetime of seizures and other serious consequences. While most of the 26 mice that received transplanted glial stem cells still died, a group of six lived far beyond their usual lifespan, and four appeared to be completely cured – a first for shiverer mice. The scientists plan to gather more evidence before trying the approach in sick children.

"It's extremely exciting to think about not only treating but actually curing a disease, particularly an awful disease that affects children," said neurologist Steven Goldman, M.D., Ph.D., a leader in manipulating stem cells to treat diseases of the nervous system. "Unfortunately, right now,

we can do little more for many of these conditions besides tell parents to prepare for their kids to die."

Thousands of children with rare, fatal disorders known as pediatric leukodystrophies share a central problem with the shiverer mice: Their brain cells lack sufficient myelin, a vital fatty coating that wraps around cells in the brain like insulation around an electrical wire. Myelin coats long sections, known as axons, of brain cells called neurons, and without it, the electrical signaling between neurons becomes sluggish and muddied, causing a variety of symptoms. Myelin loss is at the heart of multiple sclerosis, and also plays a role in the symptoms of diabetes, high blood pressure, and other diseases.

In children, diseases of myelin go by a host of names but share the same features: a childhood and young adulthood that may include weakness, difficulty standing or walking, seizures, dementia, paralysis, and ultimately, death. These diseases, which include Tay-Sachs, Krabbe's, Canavan's, Pelizaeus-Merzbacher, Vanishing White Matter Disease and a host of others are each rare, but collectively they kill thousands of children every year. Just last week, Lorenzo Odone, whose battle with one such disease, adrenoleukodystrophy, was featured in the film Lorenzo's Oil, passed away. Currently there is no treatment for any of these conditions.

Goldman and first author and scientist Martha Windrem have been working on shiverer mice for more than a decade. In work published in 2004 in Nature Medicine, the team restored myelin in a widespread area of an animal's brain, by injecting human stem cells that eventually become oligodendrocytes, the cells that produce myelin. In those earlier experiments, the team attempted to repair cells in only certain parts of the brain. Although the methods were effective, the treatment didn't actually improve the health of the mice.

In the latest work, the team took advantage of the routes that cells commonly take to migrate from one region of the brain to another. They injected approximately 300,000 human stem cells into the brain of each mouse, choosing five particular spots because of their ability to serve as launch pads of sorts for stem cells to migrate and colonize the entire brain and spinal cord.

And that's just what happened in some of the mice. In just two months, the glial stem cells multiplied and spread, covering nerve cells in almost the entire central nervous system, exactly mirroring their distribution in the brains of healthy mice. For several months after that, the cells produced myelin that coated nerve cells throughout the entire brain and spinal cord; from then on, the brain cells functioned normally, conducting impulses as quickly as in normal mice.

Not all of the transplanted mice fared well. Of 26 mice treated with stem cells, about three-quarters died, typically from seizures, within a couple of weeks of their untreated counterparts. But the six treated mice that lived longer recuperated to a degree hardly thought possible. The four mice that still survived one year after treatment improved rapidly, had no seizures, and were practically free of symptoms.

"We kept expecting them to die. Not only did they not die, but they improved day by day," said Goldman, who is director of the Center for Translational Neuromedicine and professor of Neurosurgery and Neurology.

The stem cells established themselves and spread throughout the brain with similar success in all the transplanted mice, including the ones that died near the time of their untreated counterparts. So why did some mice live longer? Goldman believes it was a race against time: Many of the mice were so sick that constant seizures killed them before the stem cells could take hold, propagate, spread, and remyelinate brain cells.

Source: University of Rochester