MedicalXpress

Team discovers genetic dysfunction connected to hydrocephalus

July 17 2014

The mysterious condition once known as "water on the brain" became just a bit less murky this week thanks to a global research group led in part by a Case Western Reserve researcher. Professor Anthony Wynshaw-Boris, MD, PhD, is the co-principal investigator on a study that illustrates how the domino effect of one genetic error can contribute to excessive cerebrospinal fluid surrounding the brains of mice—a disorder known as hydrocephalus. The findings appear online July 17 in the journal *Neuron*.

Cerebrospinal fluid provides a cushion between the organ and the skull, eliminating waste and performing other functions essential to neurological health. Within the brain there are four spaces—or ventricles—where cerebrospinal fluid flows. Hydrocephalus can be damaging when excessive cerebrospinal fluid widens spaces between ventricles and creates pressure to brain tissue. In humans, hydrocephalus can cause a host of neurological ailments: impairment of balance and coordination, memory loss, headaches and blurred vision, and even damage to the brain.

"Most of the time, hydrocephalus is caused by some sort of physical blockage of the flow of cerebrospinal fluid, so called obstructive hydrocephalus. We demonstrated instead that malfunction of specific genes—the Dishevelleds (Dvl genes)—triggered hydrocephalus in our mouse models. These genes regulate the precise placement and alignment of cilia within ependymal cells that move cerebrospinal fluid throughout the brain," said Wynshaw-Boris, MD, PhD, James H. Jewell

MD '34 Professor of Genetics and Chair, Department of Genetics and Genome Sciences, Case Western Reserve University School of Medicine. "This discovery paves the way for more focused research to determine if similar mechanisms can cause hydrocephalus in humans."

Scientists are still at the most nascent stages of understanding different causes and kinds of hydrocephalus. In some instances, the root sources are genetic; in others, the fluid accumulation is attributed to complications of premature birth. This project illuminates one way in which genetic influences contribute to the condition.

Wynshaw-Boris began this collaborative research while a professor in pediatrics at the Institute for Human Genetics and the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at the University of California at San Francisco (UCSF) before coming to Case Western Reserve in June 2013. For this hydrocephalus project, he joined fellow principal co-investigator, Arturo Alvarez-Buylla, PhD, professor of neurological surgery, and the Heather and Melanie Muss Endowed Chair, Department of Neurological Surgery, UCSF, in conducting research that proved in mice that Dvl genes regulate the placement and polarity of cilia in ependymal cells that line the ventricles of the brain.

A cilium is a slender protuberance projecting from many cells. In the ependymal cells, multiple cilia protrude from each cell as a bundle or patch, which resembles a horse's tail when beating to move cerebrospinal fluid efficiently. Each cilium must be anchored, sized and shaped correctly, properly placed and aligned in relation to other cilia within the same cell, and the alignment of cilia between cells is also necessary so that the cilia beat with precision to achieve proper movement of fluid in the right direction. It is all about excellent organization: the wrong size, shape or angle of rotation of the bundle of cilia will impede the smooth and appropriate directional flow of the cerebrospinal fluid.

The work in mice by Shinya Ohata, PhD, and Jin Nakatani, PhD, co-first authors who worked in the Alvarez-Buylla and Wynshaw-Boris labs, respectively, and their colleagues demonstrated how normal versus Dvl-deficient mice fared in terms of cilia function. They examined cilia from the ependymal cells of normal mice and found the cilia to be well organized and correctly placed within and between ependymal cells. Investigators even viewed in real time through fluorescent imaging the intricacy with which well-orchestrated cilia swayed to move fluid along in a normal fashion.

The Dvl-deficient mice featured cilia that were disorganized and placed incorrectly and because their polarity was disrupted, and in turn, smooth fluid flow was missing. One group of mice was deficient for five of six copies of Dvl genes throughout the development of the brain, and the other set of mice had the same Dvl deficiency induced only as adults. The Dvl-deficient mice had fairly normal brain development throughout maturation from birth to adulthood, but once they were adults, hydrocephalus set in. The organization of ependymal cells, the numbers of basal bodies and cilia, and the frequency of cilia movement were normal in these Dvl-deficient mice, but the polarities in the arrangement of cilia within and between ependymal cells were defective, due to defective polarities of the basal bodies that anchor the cilia. The beating cilia lacked the coordination and capacity to move cerebrospinal fluid effectively. Fluorescent imaging revealed the sluggish flow of cerebrospinal fluid in the Dvl-deficient mice.

In the other group of mice, the normal organization and polarity of cilia changed when Dvl gene deficiency was induced as adults. The once normal placement of cilia bundles within ependymal cell began to shift in these mice in a way that distorted cilia beating and the movement of cerebrospinal fluid, causing hydrocephalus. This finding revealed that Dvl gene activity was required to maintain the structure that supported appropriate polarity in cilia beating.

"If the basal anchor of all cilia is aligned and pointing in the same direction, the cilia will be properly polarized and coordinated in their movements," Wynshaw-Boris said. "On the other hand, if the basal body anchor is not aligned properly, there are going to be problems with polarity of the cilia and ciliary bundles. Ultimately, this results in the cilia beating in wrong directions and not moving cerebrospinal fluid."

These results demonstrate that continually functioning Dvl genes are required for proper planar cell polarity of motile cilia in ependymal cells.

"Our findings suggest that this critical function of Dvl genes may play a key role in the movement of cerebrospinal fluid to prevent the development of hydrocephalus," Wynshaw-Boris said. "Identifying a new cause for hydrocephalus in an animal model will stimulate further scientific investigation to learn if this planar cell polarity pathway is involved in human hydrocephalus."

Provided by Case Western Reserve University