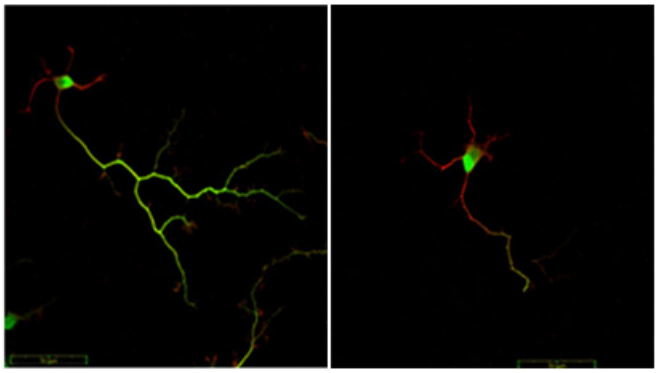
Gender influences symptoms of genetic disorder

7 February 2014, by Michael C. Purdy



A mutation in the gene that causes a human condition, neurofibromatosis type 1 (NF1), leads to shorter nerve cell branches (right) in the back of the eyes of female mice. The shorter branches, not seen in male mice with the mutation, make the cells more vulnerable. This may explain why girls with NF1 are more at risk of vision loss from brain tumors.

(Medical Xpress)—A genetic disorder that affects about 1 in every 2,500 births can cause a bewildering array of clinical problems, including brain tumors, impaired vision, learning disabilities, behavioral problems, heart defects and bone deformities. The symptoms and their severity vary among patients affected by this condition, known as neurofibromatosis type 1 (NF1).

Now, researchers at Washington University School of Medicine in St. Louis have identified a patient's gender as a clear and simple guidepost to help health-care providers anticipate some of the effects of NF1. The scientists report that girls with NF1 are at greater risk of vision loss from brain tumors. They also identified gender-linked differences in male mice that may help explain why boys with NF1 are more vulnerable to learning disabilities.

"This information will help us adjust our strategies for predicting the potential outcomes in patients with NF1 and recommending appropriate treatments," said David H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor of Neurology, who treats NF1 patients at St. Louis Children's Hospital.

The findings appear online in the *Annals of Neurology*.

Kelly Diggs-Andrews, PhD, a postdoctoral research associate in Gutmann's laboratory, reviewed NF1 patient data collected at the Washington University Neurofibromatosis (NF) Center. In her initial assessment, Diggs-Andrews found that the number of boys and girls was almost equal in a group of nearly 100 NF1 patients who had developed brain tumors known as optic gliomas. But vision loss occurred three times more often in girls with these tumors.

With help from David Wozniak, PhD, research professor of psychiatry, the scientists looked for an explanation in Nf1 mice (which, like NF1 patients, have a mutation in their Nf1 gene). They found that more nerve cells died in the eyes of female mice, and they linked the increased cell death to low levels of cyclic AMP, a chemical messenger that plays important roles in nerve function and health in the brain. In addition, Wozniak discovered that only female Nf1 mice had reduced vision, paralleling what was observed in children with NF1.

Two previous studies have shown that boys with NF1 are at higher risk of learning disorders than girls, including spatial learning and memory problems. To look for the causes of this gender-related difference, the scientists first confirmed that Nf1 mice had learning problems by testing the ability of the mice to find a hidden platform after training. After multiple trials, female Nf1 mice quickly found the hidden platform. In striking contrast, the male Nf1 mice did not, revealing that they had deficits in spatial learning and memory.

When the researchers examined the brain regions involved in learning and memory in the Nf1 mice, they identified biochemical abnormalities in the males but not in the females.

"We're currently working to determine whether differences in the sex hormones are responsible for these abnormalities in vision and memory," Gutmann said. "We're talking about a disorder in young kids and in mice, where we normally would not expect sex hormones to play a major role, but we can't rule them out yet."

If hormones are responsible for these gender-linked distinctions in NF1, treatments that block hormonal function may be an option for use in patients with NF1, Gutmann added.

"Moreover, these studies identify sex as one important factor that helps to predict clinical outcomes, such as vision loss and problems in cognitive function, in children with NF1," Gutmann said. "Further understanding of the interplay between sex and NF1 may change the way we manage individuals with this common brain tumor predisposition syndrome."

More information: "Sex is a major determinant of neuronal dysfunction in Neurofibromatosis Type 1." Diggs-Andrews KA, Brown JA, Gianino SM, Rubin JB, Wozniak DF, Gutmann DH. Ann Neurol. 2013 Dec 27. DOI: 10.1002/ana.24093. [Epub ahead of print]

Provided by Washington University School of Medicine in St. Louis

APA citation: Gender influences symptoms of genetic disorder (2014, February 7) retrieved 28 April 2021 from https://medicalxpress.com/news/2014-02-gender-symptoms-genetic-disorder.html

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