Scientists find cancer-causing virus in the brain, potential connection to epilepsy

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Researchers at Shriner's Hospital Pediatric Research Center at the Temple University School of Medicine, and the University of Pennsylvania have evidence linking the human papillomavirus 16 (HPV16) – the most common cause of cervical cancer – to a common form of childhood epilepsy. They have shown for the first time that HPV16 may be present in the human brain, and found that when they added a viral protein to the brains of fetal mice, the mice all demonstrated the same developmental problems in the cerebral cortex associated with this type of epilepsy, called focal cortical dysplasia type IIB (FCDIIB). The findings suggest that the virus could play a role in the development of epilepsy.

The results also mean that doctors may have to re-think their approach to treating this type of epilepsy, and perhaps consider other therapeutic options related to HPV, an infectious disease.

"This is a novel mechanism, and it fills a gap in our understanding about the development of congenital brain malformations," said Peter Crino, MD, PhD, Professor of Neurology at Temple University School of Medicine, and a member of Shriner's Hospital Pediatric Research Center, and the senior author of a recent report in the Annals of Neurology.

"If our data are correct, future treatment of cortical dysplasia could include targeted therapy against HPV16 infection, with the goal of halting seizures. Identifying an infectious agent as part of the

pathogenesis of brain malformations could open up an array of new therapeutic approaches against various forms of epilepsy."

FCDIIB is a developmental malformation in the cerebral cortex, the area of the brain that plays key roles in thought, perception and memory. It is a common cause of both pediatric and adult epilepsy – especially difficult-to-treat forms of epilepsy – and it is thought to occur in the womb during early brain development. The condition is characterized by a disorganized cellular structure and enlarged, "balloon cells." Current treatments include surgery and medication.

Balloon cells contain a signaling cascade called the mammalian target of rapamycin complex 1 (mTOR1), which is important for cellular growth, proliferation and division, particularly in brain development. Other scientists have recently found the mTOR pathway is activated by the HPV16 E6 oncoprotein.

While there had never been any studies indicating that HPV16 could infect the brain, Dr. Crino saw a potential connection. "This is a sporadic, congenital brain malformation associated with mTOR signaling with no genetic predisposition," he said. "Based on various cellular and cell signaling similarities between cervical dysplasia and focal cortical dysplasia, this led me to a hypothesis that the HPV protein could be detected in FCDIIB."

To find out, the investigators first examined FCDIIB tissue samples from 50 patients for evidence of the HPV16 E6 protein. They found that all of the samples were positive for the protein in the balloon cells, but not in regions without balloon cells or in 36 control samples from healthy individuals.

They next examined the samples' genetic material by several sophisticated molecular techniques to look for evidence of HPV16 E6,

and compared the findings to tissue from healthy controls and tissue from patients with different types of brain malformations and epilepsy. Again, every sample of FCDIIB was found to contain HPV16 E6 protein, whereas the control specimens and tissue from other types of dysplasia and conditions did not.

Finally, in a series of experiments, the scientists painstakingly delivered the E6 protein into the brains of fetal mice. "If E6 is the causative element for HPV cervical dysplasia and focal cortical dysplasia, putting the protein into a fetal mouse brain should disrupt the cortical development," Dr. Crino explained. When the scientists did this, they found that the fetal mouse brains did indeed develop brain malformations.

Dr. Crino plans to investigate other forms of cortical dysplasia to see if HPV or related viral proteins can be found. He and his team aren't sure how the virus gets into the brain, but their results suggest that an HPV infection in the placenta could be one possible path. The exact mechanism by which HPV16 might cause a malformation and epilepsy remains to be determined. He acknowledged several potential implications from the findings.

"We are going to have to think about this epidemiologically as an infectious disease, not a genetic disorder. In terms of prevention, with current HPV vaccination, we have a potentially modifiable disease," he said. "In addition, if in fact this type of epilepsy represents a disorder of mTOR signaling, then one strategy could be, rather than treating the patients with anti-epileptic drugs, is to perhaps use mTOR inhibitors.

"The million dollar result would be to show it is possible to induce a brain malformation with an E6 infection, and the animal develops epilepsy," Dr. Crino said. "It would be even better if we showed that it is preventable."

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