Fragile period of childhood brain development could underlie epilepsy

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Matthew Anderson, assistant professor of pathology at Harvard Medical School and principal investigaor in the departments of Neurology and Pathology at Beth Israel Deaconess Medical Center, shown here in his lab, has conducted research linking epilepsy to brain disorders in early childhood. Courtesy of Matthew Anderson

(PhysOrg.com) -- A form of partial epilepsy associated with auditory and other sensory hallucinations has been linked to the disruption of brain development during early childhood, according to a study led by researchers at Beth Israel Deaconess Medical Center (BIDMC).

Described in today's Advance On-line issue of *Nature Medicine*, these new findings provide the first genetic link between childhood brain development and a seizure disorder that lasts throughout adulthood, and also identify a new pathway that controls how neuron circuits are "pruned" and matured.

"During early childhood - roughly between the ages of one and five - the brain undergoes a period of major circuit remodeling," explains senior author Matthew Anderson, MD, PhD, a principal investigator in the Departments of Neurology and Pathology at BIDMC. "Our discovery that a familial form of temporal lobe epilepsy can develop at this point demonstrates the fragility of the brain during this critical period."

The new findings focus on the development of synapses, the connections between brain cells.

"At birth, the brain is loaded with excitatory synapses which help make nerve cells 'fire,'" explains Anderson, who is also an Assistant Professor of Neurology and Pathology at Harvard Medical School. "However, if these excess synapses are not adequately 'pruned,' they can overgrow, leading to excessive transmission of excitatory signals and the development of pathological conditions, including learning disabilities and autism in addition to epilepsy."

Using a genetically engineered mouse model created in his laboratory, together with brain slice patch-clamp electrophysiology techniques, Anderson and his scientific team found that a mutant form of the LGI1 (leucine-rich glioma-inactivated 1) gene was preventing the normal brain development.

"The first clue was our discovery that LGI1 is not expressed until the exact time when excitatory synapses are matured," said Anderson. "We subsequently learned that the mLGI1 gene was indeed prohibiting excitatory synapses from being adequately pruned, leading to an increased excitability of circuits in the brain which left it prone to excessive synchronous discharges that are characteristic of epilepsy."

Autosomal dominant lateral temporal lobe epilepsy (ADLTE) is characterized by frequent partial seizures (two to five per month) that

are associated with auditory or other sensory auras. Tonic-clonic seizures also occur in the majority of ADLTE patients, but are infrequent, developing only about once a year.

"These partial seizures can have a significant impact on a patient's quality of life," notes Anderson. "Because patients can be disoriented and excessively tired following a seizure event, their day-to-day lives can sometimes be seriously disrupted. And when it comes to driving and other activities, there is still a real danger associated with this condition.

"One important reason to identify genetic causes of epilepsy is the hope that these discoveries will eventually lead to new therapies," he adds. "By identifying this new pathway, we may have found a new target for future drug development."

Source: Beth Israel Deaconess Medical Center