Intractable seizures halted with experimental treatment for rare pediatric 'Pretzel syndrome'

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With a better understanding of underlying mechanisms that cause a rare neurodevelopmental disorder in the Old Order Mennonite population, referred to as Pretzel syndrome, a new study reports that five children were successfully treated with a drug that modifies the disease process, minimizing seizures and improving receptive language. The study, by researchers including experts from the Perelman School of Medicine at the University of Pennsylvania, appears in the journal *Science Translational Medicine*.

The disease - PSME or polyhydramnios, megalencephaly, and symptomatic epilepsy syndrome, commonly called Pretzel syndrome - is caused by a double-deletion of a specific gene that encodes for STRADA. About 4 percent of Old Order Mennonite individuals in Ohio, Pennsylvania and New York have a single copy of the deleted gene. When a double-deletion occurs, the loss of STRADA causes an activation of mTORC1 and, subsequently, the kinase p70S6K. This causes intractable seizures and results in limited cognitive development and language function, leaving PSME patients wheelchair-bound, mute and completely dependent.

When five children, ranging from 8 months old to nearly 5 years old, were given doses of a drug that inhibits mTOR, the drug Sirolimus (rapamycin) significantly reduced seizures. Four of the five patients have been seizure free for the last year; previously no PSME patients had

achieved freedom from seizures, even while on anti-epileptic medication. Starting the drug by three months of age seemed to stave off seizures; one patient who started treatment early had a single seizure and another has had no seizures.

The use of this drug in Pretzel syndrome patients stems from earlier research showing that sirolimus was an effective treatment for a related and more common disorder, tuberous sclerosis complex (TSC), which is also associated with seizures, altered brain structure and enhanced mTOR activation.

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