Clinical trial for Rett syndrome launched

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Researchers at Children's Hospital Boston have begun a randomized, placebo-controlled trial to test a potential drug treatment for Rett syndrome, the leading known genetic cause of autism in girls. The drug, mecasermin, a synthetic form of insulin-like growth factor-1 (IGF-1), is already FDA-approved for children with short stature due to IGF-1 deficiency.

The trial, now enrolling patients, marks the beginning of a trend toward drug treatments seeking to modify the underlying causes of autism spectrum disorders, rather than just behavioral symptoms such as anxiety or aggression. It follows research in animal models, published in 20091, which suggested that raising IGF-1 levels can reverse features of Rett syndrome by enhancing maturation of synapses —the points of communication between brain cells.

"We expect that therapy that stimulates synaptic maturation will serve as a model for pharmacological treatment of not only Rett syndrome, but of other autism spectrum disorders," says Omar Khwaja, MD, PhD, the study's principal investigator and director of the Rett Syndrome Program in the Department of Neurology at Children's.

Rett syndrome, occurring almost exclusively in girls, is an X-linked neurodevelopmental disorder causing severe cognitive, motor and language problems and autistic behaviors. Other features include loss of purposeful use of the hands; repetitive, stereotyped hand movements; slowed brain and head growth; and heart-rhythm and breathing problems. Although affected children appear normal during their first

six months of life, symptoms emerge, tragically, between 6 and 18 months of age, a prime period of synaptic development.

The three-year pilot study will randomize 40 girls (aged 2 to 12) with Rett syndrome to receive the drug, known as Increlexâ (Tercica Inc., a Subsidiary of the IPSEN Group) for five months. The study will use a cross-over design, allowing girls assigned to placebo to switch to active treatment after a six-week "washout" period. The main outcome measures will be improvement in neurodevelopment and in cardiorespiratory function.

Although Rett syndrome used to be seen as a degenerative, irreversible disease, recent research indicates that brain cells aren't actually lost, and the brain is structurally normal – instead, the synapses between cells are weak, preventing brain circuits from maturing. Rett syndrome's usual cause is mutation or deletion of a gene called MeCP2, which itself controls a group of genes that regulate synaptic changes in response to input from the environment. In 2007, working with a mouse model of Rett syndrome, researchers used genetic tricks to restore MeCP2's function in the brain.2 The mice showed a striking recovery, suggesting that Rett syndrome, even when well established, might be a treatable disease – if only synapses could be built back up.

"This was an enormous intellectual proof-of-principle that we aren't wasting time thinking of therapies for girls who are already symptomatic," says Khwaja. "Before, it was thought that if there ever was a treatment, it would have to be given before symptoms appeared, and that once the disease started it couldn't be reversed."

IGF-1, the drug used in the trial, is indirectly regulated by MeCP2. It has been shown to enhance synapse maturation, and in mice missing the MeCP2 gene, treatment with IGF-1 ameliorated several features of their Rett-like disease.1

"There's been a big sea change in how Rett syndrome and other neurodevelopmental disorders are viewed," Khwaja says. "The synapses are very dynamic. They need to be stabilized, and if they don't receive the right stimulus, they'll naturally disappear. That change in paradigm has really affected the way that we look at treatments, and I think it brings a lot more hope."

The new view has already affected the way schooling and education of children with Rett syndrome are being approached. "There's more and more evidence in animals that enrichment and schooling can help synapses form and strengthen," says Khwaja. "The battle is getting the girls into appropriate educational settings. If you are repetitive, and give them ways to communicate, they actually can learn, and that's probably because you're reinforcing these synaptic connections."

More information: (1) Tropea D; et al. Partial reversal of Rett Syndrome-like symptoms in MeCP2 mutant mice. Proc Natl Acad Sci U S A. 2009 Feb 10;106(6):2029-34.

(2) Guy J; et al. Reversal of neurological defects in a mouse model of Rett syndrome. Science 2007 Feb 23;315(5815):1143-7.

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