ADHD medicine may treat symptoms of genetic movement disorder in children, new study finds

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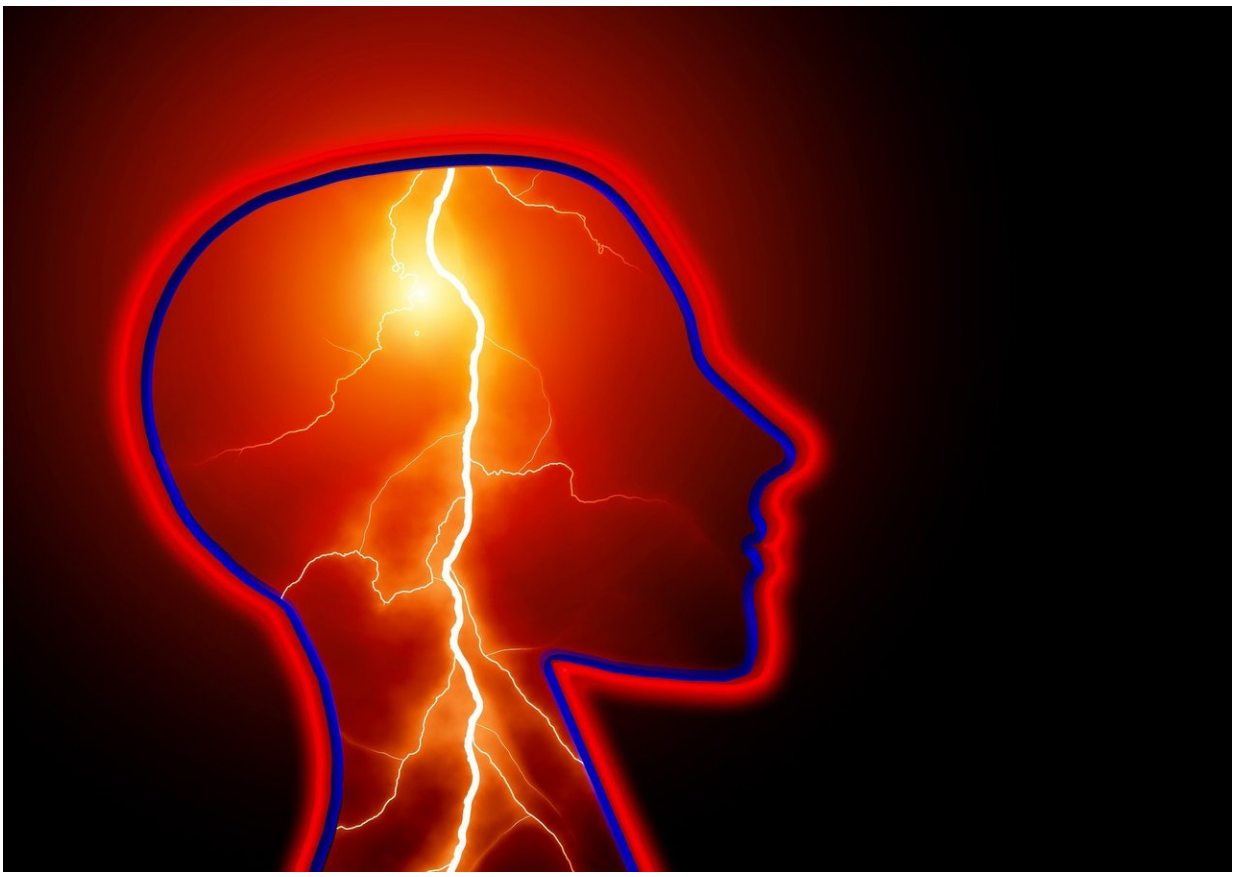

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Using a common attention deficit hyperactivity disorder (ADHD)

medication appears to help manage the symptoms of a rare and currently difficult to treat genetic movement disorder primarily found in children, according to a new study from a University of Maryland School of Medicine (UMSOM) researcher Andrea Meredith, Ph.D., and her collaborators.

The disorder, KCNMA1-linked channelopathy, named after the affected gene, can cause abnormal, involuntary movements from collapsing episodes, in which patients slump forward with their arms and legs appearing rigid. These episodes can occur up to 300 times per day, putting patients at risk of serious injury.

The researcher found that the stimulant drug lisdexamfetamine reduced these attacks and may help other accompanying symptoms, such as seizures and developmental delays, as well.

These findings were published online on December 11, 2021 in *Movement Disorders Clinical Practice*.

The researchers say their findings can help to better understand different brain regions involved with the attacks and how the disease manifests itself. While this research shows promise of specifically treating KCNMA1-linked channelopathy, there are broader implications to exploring the treatment effects on the body, potentially shedding light on the mechanisms behind other neuromuscular diseases and how to treat them.

"Sometimes the science doesn't initially lead us to the answers, it is often the patients and families themselves," said senior author Dr. Meredith, Professor of Physiology at the University of Maryland School of Medicine.

Only about 75 people so far have been identified worldwide with this

disorder, which was identified as recently as 2005. A major advance came in 2019 when it was reported anecdotally that a child suffering from the disorder was prescribed lisdexamfetamine by their neurologist, which, according to the family, seemed to help. The physician tried this stimulant medication, commonly used to treat cataplexy-related disorders; the child's symptoms resembled cataplexy, which is a sudden muscle weakness that occurs without the sufferer losing consciousness. From there, word spread to other families over social media, news media, and the disease's advocacy foundation, KCNMA1 Channelopathy International Advocacy Foundation, which was co-founded by Dr. Meredith. The buzz from the patients' families spurred neurologists, including the study authors, to test the relatively safe drug, which is approved by the U.S. Food and Drug Administration to treat ADHD.

For their study, the researchers analyzed reports of six patients treated with lisdexamfetamine. They found that the collapsing episodes were reduced about 10-fold or were completely resolved in four patients. Most patients also showed improvements in speech, school performance, concentration, and social skills, all of which can affect patients with this disease as well. None of the patients experienced seizures during the study period. The most common side effect reported was loss of appetite and difficulty sleeping.

"From the anecdotal reports we already had, we weren't particularly surprised by these findings," said Dr. Meredith. "But gathering the real-world evidence that the drug is actually working to treat the symptoms is important for clinicians who may prescribe the drug to officially diagnosed patients."

It is currently unclear how lisdexamfetamine works to treat the attacks. The gene affected in the disorder, KCNMA1, encodes a protein that makes a "channel" in brain and muscle cells. This channel lets potassium out of the cell to change its electric charge. Neurons in the brain send

messages and tell the muscles to move using these electrical signals, but the exact way this channel disruption leads to the symptoms experienced by the patients is unknown.

However, the success of lisdexamfetamine treatment in the small group of patients may provide the answers. "We have exciting mechanistic avenues to pursue as a result of this finding," said Dr. Meredith. "We do know that the drug does not directly affect the activity of the channels, so we think the drug has either a separate, or an indirect effect, on the channels."

They researchers plan to continue studies of the disorder and the drug in their mouse models.

"Rare diseases are often overlooked in research and treatment," said E. Albert Reece, MD, Ph.D., MBA, Executive Vice President for Medical Affairs, UM Baltimore, and the John Z. and Akiko K. Bowers Distinguished Professor and Dean, University of Maryland School of Medicine. "We are proud of our researchers in pursuing treatment of a rare disease that opens new doors, pushes medical boundaries, and improves the lives of those who may feel left behind."

Other authors on the study included Sotirios Keros, MD, Ph.D., and Zach Grinspan, MD, MS, of Weill Cornell Medical College; Jennifer Heim, MD, Wejdan Hakami, and Michael Kruer, MD, of Phoenix Children's Hospital; and Efrat Zohar-Dayan and Bruria Ben-Zeev, MD, of Chaim Sheba Medical Center, Israel.

More information: Sotirios Keros et al, Lisdexamfetamine Therapy in Paroxysmal Non-kinesigenic Dyskinesia Associated with the KCNMA1 -N999S Variant, *Movement Disorders Clinical Practice* (2021). DOI: 10.1002/mdc3.13394

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