New simple test detects rare fatal genetic heart condition

June 20 2024

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A team of international researchers has revealed a new, simple clinical test to detect calcium release deficiency syndrome (CRDS), a life-threatening genetic arrhythmia that causes dangerously fast heartbeats and can lead to severe complications such as sudden cardiac arrest and death.

The new diagnostic method monitors for changes in electrocardiography (ECG) after a brief period of a fast heartbeat and a pause, which can occur naturally or be induced by artificially pacing the heart.

This research was co-led by Jason Roberts, a scientist at the Population Health Research Institute (PHRI), a joint institute of McMaster University and Hamilton Health Sciences, and Wayne Chen, a scientist and professor at the Libin Cardiovascular Institute and Hotchkiss Brain Institute at the University of Calgary's Cumming School of Medicine, and published on June 20, 2024, in *JAMA*.

While 60,000 cardiac arrests occur annually in Canada, CRDS remains undetectable with standard clinical tests, often resulting in the cardiac arrests being labeled as unexplained. This gap in understanding the underlying cause prevents the delivery of optimal care to survivors and vulnerable family members who may be affected by this genetic condition.

"This novel and simple diagnostic method, which can be performed using an electrocardiogram in a broad range of clinical settings, is hopefully an important step towards improving our evaluation of initially unexplained cardiac arrest (UCA)," said Roberts, co-principal investigator of the study.

Roberts and Chen led this multi-center case-control study involving 68 study participants from 10 centers in seven countries. The participants were from four categories of heart conditions, including CRDS patients and UCA survivors.

Accompanying studies from Chen's lab revealed findings in genetic mouse models that mirrored those observed in humans. The mouse studies also provided insight into the underlying cellular mechanism responsible for this apparent ECG signature of CRDS.

"CRDS has been linked to many tragic incidents and heartbreaking stories affecting families. There have been numerous cases where patients experienced fainting episodes, but their tests showed no issues,

which led doctors to believe the fainting was not due to a dangerous heart condition. A portion of these individuals, often young and otherwise healthy, subsequently suffered sudden cardiac arrests, and some did not survive," said Roberts.

"This raised many questions in the medical community, most of which remained unanswered until Chen and his team established the existence of this rare genetic syndrome in 2021. However, the diagnosis has required specialized laboratory testing available only in research settings, making it inaccessible to most physicians and limiting the ability to care for potentially affected patients and their families."

The study marks the initial stage of Roberts and Chen's efforts in further exploring a diagnostic approach for CRDS and collecting additional data as part the ongoing PHRI DIAGNOSE CRDS trial. This trial represents a broader, international initiative aimed at strengthening their conclusions. Currently in the recruitment phase, DIAGNOSE CRDS aims to enroll 500 participants from 30 sites across 10 countries.

"We hope this test will help many families worldwide who have faced unexplained cardiac incidents or lost loved ones to them," added Roberts.

The team anticipates this simple pacing test will be incorporated into the routine diagnostic tests for initially unexplained cardiac arrest, providing hope for better outcomes and prevention of future tragedies.

"This is an important discovery because there is an urgent need for a clinical diagnostic test for CRDS," says Chen. "This will allow us to identify individuals at risk, better understand the prevalence of CRDS and, hopefully, develop treatments for the condition."

More information: A Clinical Diagnostic Test for Calcium Release Deficiency Syndrome, *JAMA* (2024). DOI: 10.1001/jama.2024.8599