Research Week 2020

Sudden Cardiac Death in Young Adults with Long-Chain 3-Hydroxyacyl CoA Dehydrogenase Deficiency (LCHADD)

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Keywords

fatty acid oxidation disorders, sudden cardiac death, stem cell research, genetic diseases, cardiology

Abstract

Long-chain 3-Hydroxyacyl CoA Dehydrogenase Deficiency (LCHADD) is an autosomal recessive defect in fatty acid oxidation that presents with hypoketotic hypoglycemia and/or hypertrophic cardiomyopathy in infancy, and recurrent rhabdomyolysis in adolescence, however, sudden cardiac death has not been a previously reported complication of LCHADD. We have conducted a case review study comparing young adult LCHADD patients who have experienced sudden cardiac arrest events (n=5) to similar patients who have not (n=5) for the purpose of evaluating associated cardiac risk factors. We reviewed medical records from ECG tests, hospitalization reports, acylcarnitine and complete metabolic panels, clinic notes, and autopsy reports. Retrospective chart review has led to no certain etiology however, electrolyte derangements, low free carnitine and elevated total to free carnitine ratios have been noted upon hospitalization in sudden cardiac arrest cases. At the time of the sudden death event, only one subject was noted to be in metabolic crisis with elevated creatine phosphokinase levels. Life threatening ventricular arrhythmias appear to be a newly recognized life-threatening complication in the adolescent and young adult age groups of LCHADD patients. The exact mechanism underlying the sudden death events are not understood and there are no current therapies. Recent advances in human induced pluripotent stem cell (hiPSC) technology has provided extraordinary progress in understanding the mechanisms in generating induced pluripotent stem cell derived cardiomyocytes. Future directions of this study seek to generate LCHAD deficient patient derived iPSC-CMs in order to assess mitochondrial function, force of contraction, oxygen consumption rates and calcium retention capacities. Assessing the disruption of bioenergetics and mitochondrial function in hiPSC-CMs will provide a meaningful exploration to understand the potential pathways that contribute toward the severe cardiac clinical manifestations observed in affected LCHADD patients who have experienced sudden cardiac death events.