

The congenital glycosylation disorder PGM1-deficiency can give rise to severe cardiomyopathy and unexpected sudden cardiac death in childhood

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INTRODUCTION: Sudden cardiac death (SCD) in the young is rare, and should always lead to suspicion of a genetic cardiac disorder. We describe a family, in which the proband was a girl at thirteen years of age deceased by sudden cardiac death in the playground. The girl, the index-patient, had short stature, cleft palate but no previous cardiac symptoms. We found an uncommon cause of restrictive cardiomyopathy, due to a congenital disorder of glycosylation (CDG), previously described to cause a variable range of usually mild symptoms, and not previously found to cause SCD as the first symptom of the condition.

METHODS: The index patient underwent postmortem genetic testing for genes known to cause SCD without a known causative agent. There was two siblings of similar phenotype as the deceased sister, why they underwent whole-exome genetic sequencing. All first-degree relatives underwent clinical examination including biochemistry panel, cardiac ultrasound, Holter-ECG and exercise stress test.

RESULTS: A genetic variant in the gene for phosphoglucomutase 1 (PGM1) was identified in these two boys and the deceased sister, all were found to be homozygous for the genetic variant NM_002633.2:c.689 G>A in PGM1. This variant has been linked to a congenital disorder of glycosylation (CDG-PGM1), explaining the clinical picture of short stature, cleft palate, liver engagement and cardiomyopathy. During follow-up one of the brothers died unexpectedly after physical exertion during daily life at the age of twelve years. The other brother fainted during similar circumstances at the age of thirteen years. Both parents and three other siblings were found to be heterozygous gene carriers without risk for the disease.

CONCLUSION: Our findings suggest that there is a need of multidisciplinary discussion and the value of genetic testing after unexpected cardiac death in the young. In the global migration period we have to be more open-minded even for uncommon diseases as well as increased amount of recessive inherited disorders. Our findings suggest that the autosomal recessive CDG-PGM1 is highly associated with life-threatening cardiomyopathy with arrhythmia or sudden cardiac death as the first symptom presenting from childhood and adolescence.