Clinical and Genetic Findings in Children Presenting With Ventricular Fibrillation as the First Manifestation of Cardiovascular Disease

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Cardiac arrest secondary to ventricular fibrillation (VF) is rare in children, representing <10% of all pediatric out-of-hospital arrests, however it may be associated with unrecognized cardiovascular disease and improved survival. Establishing a diagnosis is challenging given low survival rates, inconclusive autopsy findings, and the complexities of post-mortem genetic testing.

The authors declare that all supporting data are available within the article. In this study, we investigated 55 unrelated probands (40 males) aged 11.5±5.7 years (range 0.1–17.8 years) who presented from 1992 to 2019 to a single center with no prior evaluation for personal or familial cardiovascular disease. All had documented VF and survived to hospital in-patient admission allowing for initial and longer-term (≥3 months) clinical evaluation to determine an underlying cardiac etiology. Data are expressed as mean±SD, and analysis of variance was used for comparison between groups. The Boston Children's Hospital Institutional Review Board approved the study. There was no difference in the nature of activities nor age at the time of cardiac arrest: at rest (n=16; 12.2±5.9 years), light activities (n=15; 9.3±7.4 years), or exercise (n=20; 12.8±3.2 years); P=0.17. Activity was unknown in 4 cases. A family history of sudden cardiac death was present in 3 families. Cardiovascular investigations (Figure A) and genetic testing were performed as considered clinically appropriate, and diagnoses made based on contemporaneous criteria. Those with no clear diagnosis were considered to have idiopathic VF.

Investigations, diagnosis at time of latest evaluation and genetic testing are displayed in Figure A-C. One patient died secondary to acute lymphocytic myocarditis, and 7 suffered varying degrees of neurological damage. Follow-up for all patients was 6.0±4.8 years, with 29 under active management at our institution. The initial diagnosis was revised in 2; a female child initially diagnosed with long-QT syndrome was later diagnosed with triadin knock out syndrome based on identification of a homozygous loss of function variant in triadin,2 and an adolescent male initially thought to have myocarditis represented with a recurrence and associated in-hospital cardiac arrest 5 years later. He was diagnosed with left dominant arrhythmogenic cardiomyopathy with a frameshift variant identified in desmoplakin (Figure D).3

The diagnosis was idiopathic VF in 25 patients, with no difference in age compared with others (11.3±5.3 vs 11.7±6.3 years; P=0.82) nor nature of activities at the...
Figure. Cardiovascular and genetic investigations and findings.
A. Clinical investigations and genetic testing performed on 55 patients at initial evaluation. B. A bar chart represents the number of patients within each diagnostic category, color coded as per the guide in panel B. C. The number of patients who underwent genetic testing is shown, together with the number of pathogenic or likely pathogenic variants and variants of unknown significance. D. Pathogenic and likely pathogenic variants identified in 14 patients considered concordant with the clinical diagnosis and therefore implicated in the underlying disease process. ACM-ARVC indicates arrhythmogenic cardiomyopathy – arrhythmogenic right ventricular cardiomyopathy; ACMG, American College of Medical Genetics and Genomics; ACM-LD, arrhythmogenic cardiomyopathy – left dominant; CALM, calmodulinopathy; Catheter, hemodynamic catheterization and angiography; CPVT, catecholaminergic polymorphic ventricular tachycardia; echo, echocardiogram; EPINEP, epinephrine; ER, early repolarization; EST, exercise stress test; Gen T, genetic testing; HCM, hypertrophic cardiomyopathy; LQTS, long-QT syndrome; LVNC, left ventricular non-compaction; MRI, magnetic resonance imaging; MVP, mitral valve prolapse; P/LP, pathogenic/likely pathogenic; PM, moderate; PP, supporting; PS, strong; PVS, variant of unknown significance; and WPW, Wolff-Parkinson-White syndrome. *Whole exome sequencing with parental testing. †Not considered concordant with diagnosis because of lack of segregation (see text for details).
time of arrest. Over 6.8±5.0 years follow-up, 7 (28%) developed non-specific findings including left ventricular dilatation (2) or dysfunction (1), monomorphic ventricular tachycardia (2), morphological repolarization abnormalities (1), and atrial fibrillation (1). No specific diagnosis was made in any patient. Implantable cardioverter defibrillators were used in 46 patients; 9 patients did not receive implantable cardioverter defibrillators because of Wolff-Parkinson-White (2); anomalous right coronary artery (1); severe neurological injury and family preference (3); death (1); and extreme young age (2). During follow-up appropriate implantable cardioverter defibrillators therapies occurred in 2 patients with idiopathic VF compared with 11 with a specific diagnosis. Intermittent early repolarization was seen during follow-up in 6, 2 of whom had other non-specific findings, however no association with subsequent arrhythmia was evident. In 35 families screened, clinically affected individuals were identified in 6 (17%), including 1 family with a prior history of sudden death and multiple living members with cardiomyopathy, however the neurologically devastated proband had normal cardiac evaluation during 7 years follow-up.

Genetic testing was performed in 35 patients. In 14, a pathogenic or likely pathogenic variant concordant with the associated phenotype was identified (Figure D), representing 40% (14/35) of all those tested and 67% (14/21) of those with an evident phenotype. Importantly, in 2 young males who suffered exertional cardiac arrest (Figure D, #43 and #50), variants previously associated with catecholaminergic polymorphic ventricular tachycardia were identified in calmodulin 1 (CALM1) and cardiac ryanodine receptor (RYR2) respectively; clinically both had sinus bradycardia but neither had ventricular ectopy nor polymorphic ventricular tachycardia on exercise testing. Two other patients had notable genetic findings: a 15-year-old male with idiopathic VF had an SCN5A variant (p.R814Q) previously reported as a homozygous variant in a Brugada syndrome/arrhythmogenic cardiomyopathy overlap condition,4 however is present 7 times (minor allele frequency [MAF] 0.000025) in the Genome Aggregation database. Another variant at the same residue (p.R814W) segregates with a dilated cardiomyopathy phenotype in 16 members of a single family.5 Combining clinical and genetic investigations, a diagnosis was made in 30 (55%).

In conclusion, idiopathic VF is the most common diagnosis following unheralded cardiac arrest in children, seen in 45% of cases; over follow-up a proportion develop non-specific findings but with no clear evidence to date of a unifying diagnosis. Detailed evaluation including clinical and genetic investigations results in a definitive diagnosis in the majority of pediatric VF survivors.

ARTICLE INFORMATION

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