Addressing the diagnostic and therapeutic challenges in inheritable arrhythmia syndromes: with emphasis on the pediatric population

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Chapter 8

Idiopathic Ventricular Fibrillation in Two Infants, Not Always Idiopathic on Follow-Up

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Introduction

Idiopathic ventricular fibrillation (IVF) is defined as spontaneous ventricular fibrillation (VF) in the absence of identifiable cardiac and extracardiac abnormalities responsible for the arrhythmic event.\textsuperscript{1} IVF accounts for 5%-10% of out-of-hospital survivors of cardiac arrest.\textsuperscript{2,3} The mean age of IVF patients is 35-40 years and 70%-75% are male.\textsuperscript{4} Implantable cardioverter defibrillator (ICD) forms the mainstay of treatment\textsuperscript{1} and the youngest reported case of IVF is a 7-year old male treated with ICD.\textsuperscript{5}

The recent progress in the understanding of genetic disorders has disclosed evidence that genetically transmitted abnormalities underlie a larger proportion of cardiac arrests than previously appreciated.\textsuperscript{6} It should also be realized that, although mechanical cardiac function may be (grossly) normal, patients with VF might have discrete genetic or structural abnormalities which are currently unidentifiable.\textsuperscript{7} We report about two infants who recently presented to our hospital with aborted out-of-hospital cardiac arrest. Initial diagnostic evaluation failed to identify an underlying cause for VF in both cases. However, on follow-up, one of the cases developed evidence of structural heart disease.

Case Reports

Case 1

A 12-month old previously healthy Black male presented with sudden cardiac arrest at home. On the day of the incident, he had been awoken from his mid-day nap when his father started using a noisy food mixer. He had apparently run towards his father but became limp on the way. His father had started cardiopulmonary resuscitation with telephonic advice from the emergency services. The child was noted to be in VF by the ambulance team. After successful resuscitation and defibrillation, he was admitted to our intensive care unit. His prenatal, neonatal and early infantile histories were unremarkable. There was no family history of cardiac disorders or sudden unexplained death.

Chest radiography on admission was within normal limits. Electrocardiography (ECG) was normal for age with a heart rate of 105 bpm, PR interval of 130 ms, QRS duration 74 ms, QT duration 312 ms and QTc 412ms (Figure 1: Case 1). A 24-hour ECG was normal and did not reveal any arrhythmias. Biochemical profile revealed normal electrolytes, normal blood sugar and a mild metabolic acidosis. The blood culture, metabolic screen and urine toxicology screen were negative. An electroencephalogram ruled out epileptic foci. An echocardiogram demonstrated normal cardiac structure and function. Electrophysiological study and coronary angiography were both normal. In view of the possibility of congenital arrhythmia syndromes, he was subjected to an epinephrine challenge test and flecainide test which were both negative. Genetic screening for congenital long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) was negative. Cardiac screening of both parents with echocardiogram, exercise test and 24-hour ECG was normal. Having ruled-out the known cardiac and non-cardiac causes of VF, a diagnosis of IVF was made.
During the following weeks in hospital, the child was stable and had no further arrhythmias. He was implanted with an ICD 4 weeks after the VF episode, at the age of 13 months. The ICD patch electrode was positioned subcutaneously in the left lateral thorax, the ventricular bipolar lead epicardially on the right ventricular apex, and the ICD generator submuscularly in the right upper abdomen. Follow-up for 3.5 years with ECG and echocardiogram was normal with no further ventricular arrhythmias and no evidence of congenital arrhythmia syndromes or structural heart disease. He also demonstrated age-appropriate neurocognitive and psychomotor development.

**Case 2**

A 9-month old female was being put to bed by her mother when she had a cardiac arrest. VF was detected by the ambulance team and the child was successfully resuscitated and defibrillated. The child had had history of vomiting and diarrhoea for two days prior to the incident but was apparently afebrile and active. She was given oral rehydration solution under the physician’s advice. Her past medical history was uneventful. She was the second-born child of healthy non-consanguineous Caucasian parents. On interrogation, there was a history of sudden death in the family. The older male sibling of the patient had died suddenly at the age of 3 years, in 2005. Post-mortal metabolic investigations had not revealed a cause for his death. The cardiac examination of both parents including an echocardiogram, exercise and 24-hour ECG at that time had been normal.

On admission to the intensive care unit, the child underwent a complete diagnostic work-up. The basic biochemical profile, acute inflammatory markers and cerebrospinal fluid analysis were within normal limits. Blood bacterial culture and viral serology were negative. The ECG on admission (Figure 1: Case 2) showed a heart

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**Figure 1.** Twelve-lead ECG of case 1 (male, 12 months) and case 2 (female, 9 months) on admission.
rate of 150 bpm, PR 107 ms, QRS 65 ms, QT duration 238 ms and QTc 376 ms, and a later 24-hour ECG was also normal for age. Echocardiography revealed normal heart structures with slightly decreased function of the ventricles which normalised within 48 hours of the cardiac arrest. CT scan of the brain was normal. Angiography ruled out any coronary artery abnormalities and the myocardial biopsy was normal. Electrophysiological study of the heart was normal. Epinephrine challenge test and flecainide test were negative. Genetic screening for LQTS revealed a variant in the KCNQ1 gene. This variant had not been described earlier and its clinical relevance was unknown. Considering the normality of the ECG and a negative epinephrine challenge test, the genetic variant was deemed unlikely to be pathogenic in the child. An ICD was implanted a month after the initial event. The patient was discharged home a few days after the procedure, at the age of 10 months.

Follow-up at 3-monthly intervals with ECG and echocardiogram was normal and there were no further ventricular arrhythmias. However, at the age of 19 months, the child was readmitted with signs of cardiac failure following an episode of gastroenteritis. Echocardiography at this time revealed a dilated cardiomyopathy (DCM). In view of this development, further investigations were carried out to elucidate an underlying cause for the DCM such as neuromuscular disorders and inborn errors of metabolism. Muscle biopsy and metabolic screen were normal. The presence of genetic factors that may underlie the DCM are currently being investigated in this patient.

Discussion

The first consensus statement on IVF published in 1997\(^1\) states that IVF is a diagnosis of exclusion and several noninvasive and invasive tests have to be performed to rule out structural heart disease before the diagnosis is made. Today, an accurate definition and diagnosis of IVF is still elusive, especially with a myriad of genomic and proteomic information becoming available on the etiology of sudden cardiac death. The recent progress in the understanding of genetic disorders has disclosed evidence that genetically transmitted abnormalities such as Brugada Syndrome (BS), LQTS and CPVT underlie a larger proportion of cardiac arrests than previously appreciated.\(^6\) A considerable number of patients initially classified as IVF are now believed to have an identifiable cause for the electrical instability and it is speculated that further scientific advances will pave the way for better understanding of the etiopathophysiology of IVF.

Late manifestations of structural heart disease in IVF patients have been reported in the past.\(^8\) However, VF as the initial presentation of DCM in infancy is extremely rare and even unheard of. The second case reported here with presumed IVF developed evidence of DCM 10 months after the initial VF episode; the underlying etiology of the DCM is currently being investigated. A multicenter study on DCM in 1426 children has reported that 34% of all cases had an identifiable cause for the DCM while the remaining were idiopathic.\(^9\) The most common causes were myocarditis and neuromuscular diseases followed by familial DCM, inborn errors of metabolism and malformation disorders. Our case report highlights the relevance of careful follow-up
and monitoring of all patients with an unidentifiable cause for VF, knowing the fact that IVF is a rapidly evolving amalgam of diseases.

An acoustic trigger for VF in case 1 suggests a non-idiopathic origin of the VF, especially LQTS. However, a normal ECG, a negative epinephrine challenge test and the absence of known LQTS mutations are pointers against a diagnosis of LQTS. It is known that approximately 25% of families with a strong clinical probability of LQTS will have a negative genetic test result because not all mutations responsible for LQTS have been identified, once again stressing the importance of close follow-up in these patients. Equally important would be extensive parent evaluation in the wake of a possible genetic cause for the IVF.

Sudden infant death syndrome (SIDS) is a common diagnosis in children who have died in the first year of life. Despite several hypotheses focussing on cardiac and respiratory mechanisms underlying the sudden death, the view remains that SIDS is multifactorial and that many different mechanisms including metabolic and genetic factors can lead to SIDS. Congenital arrhythmia syndromes, especially LQTS have been cited to be responsible for a considerable number of SIDS cases.

IVF patients have a high recurrence rate of arrhythmias and ICD remains the cornerstone in the prevention of sudden cardiac death in both adult and pediatric patients. Novel ICD implantation techniques have been developed for the pediatric population with resultant reduction in complications during implantation and follow-up. A recent multicenter study on pediatric ICD implantations has shown that congenital heart diseases, cardiomyopathies and structurally normal hearts with primary electrical diseases are the major indications for ICD in this population. In both cases reported here, there was no recurrence of ventricular arrhythmias on follow-up.

Conclusions

Idiopathic ventricular fibrillation can be seen even in very young children. Irrespective of the age group, a strict protocol for the exclusion of the known cardiac and non-cardiac causes of ventricular fibrillation should be adhered to. Careful follow-up is necessary in order not to miss any evidence of structural heart disease or congenital arrhythmia syndromes that might develop at a later time. ICD provides effective secondary prevention of sudden death in these young survivors of cardiac arrest.

References