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Case Report

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Successful pregnancy in a high-risk catecholaminergic polymorphic ventricular tachycardia patient

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Abstract

Objective: To report the case of a successful pregnancy outcome in a severely symptomatic woman affected by catecholaminergic polymorphic ventricular tachycardia (CPVT) carrier of a novel variant in ryanodine receptor 2 (RYR2) followed by a review of the current literature.

Case: A 27-year-old primigravida affected by CPVT was referred to our tertiary care hospital after an implantable cardioverter defibrillator (ICD) shock. The patient also received medical treatment with metoprolol and flecainide. A healthy baby was born by Cesarean section at 31 weeks after the onset of preterm labor and premature rupture of membranes. CPVT is a rare inherited cardiac condition characterized by episodic polymorphic ventricular arrhythmias with a structurally normal heart. These are usually triggered by exercise or emotional stress and can lead to syncope or even sudden cardiac death. Treatment of this condition comprises betablockers in isolation or in addition to other antiarrhythmics, left cardiac sympathetic denervation and/or ICD.

Conclusion: This case illustrates the importance of a multidisciplinary approach in this clinical scenario and the benefits of an optimization of the medical treatment, and demonstrates that, even in severely affected patients, a successful pregnancy is possible under close control. However, the risk of arrhythmic events and the course of pregnancy remain largely unknown in patients with CPVT, and further investigation is needed.

Keywords: Catecholaminergic polymorphic ventricular tachycardia (CPVT), cardioverter defibrillator (ICD), pregnancy.

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare heart rhythm disorder with no associated structural heart disease ("channelopathy") in which tachycardia episodes are usually triggered by physical exercise or emotional stress. These episodes can lead to severe outcomes such as syncope and sudden cardiac death, commonly in childhood or adolescence. Affected patients may have a family history of juvenile sudden death or stress-induced syncope. CPVT may also present sporadically as a de novo mutation in individuals with no family history. CPVT occurs with similar frequency in males and females, but males are more likely to present at an earlier age (in childhood or adolescence), while females are more likely to present at an older age (20 years, mean).[1]

Given the low prevalence and the previously reported poor prognosis of this condition, there is little information regarding the management of pregnancy in these patients.

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Case

We present a successful pregnancy of a 27-year-old primigravida with CPVT diagnosis. She was diagnosed at the age of 13 after a 4-year history of recurrent syncope related to emotional stress and was subsequently started on betablockers (atenolol). She had neither family history of sudden death nor suspected CPVT. At the age of 19, she suffered an episode of aborted sudden cardiac death (cardiorespiratory arrest and successful cardiopulmonary resuscitation) and an intravascular implantable cardioverter defibrillator (ICD) was subsequently implanted. During follow-up, ICD interrogation showed three appropriate discharges due to polymorphic ventricular tachycardia (VT) episodes.

In addition, a previously non-described variant in a protein encoding exon (p.Ser166Pro) in RYR2 (ryanodine receptor 2) gene of unknown significance was found using a Next Generation Sequencing test. Unfortunately, because of this, pre-implantation diagnosis was not considered while undergoing an in vitro fertilization (IVF) process due to unexplained infertility. However, later on in her pregnancy, genetic study results were reanalyzed and following the American College of Medical Genetics and Genomics (ACMG) criteria, this variant, located in one of the described hotspots of RYR2 gene, was considered likely pathogenic. Diagnosis of CPVT was clinically ruled out in both parents and cascade screening allowed to confirm a de novo presentation on our patient.

Once her pregnancy was confirmed and regarding the well-known risk of intrauterine growth restriction associated with most betablockers, atenolol was changed to metoprolol 50 mg twice a day. However, at 13+5 weeks of gestation, our patient suffered a new appropriate ICD shock due to polymorphic VT and decision was then made to add flecainide (50 mg twice a day) to her treatment. Due to her high risk, she was referred at this time to our center for close pregnancy follow-up.

The rest of her pregnancy remained uneventful from a cardiac perspective. As main non-cardiac issues, our patient attended emergency services for abdominal discomfort and a shortened cervix was found (24 mm, negative funnel) at 23 weeks of gestation managed with intravaginal progesterone (200 mg daily). She also had an episode of anxiety and unspecific abdominal pain at 28 weeks that required a short hospital admission for maternal-fetal monitoring. Fortunately, ultrasound scans performed during her pregnancy showed adequate biophysical profiles and amniotic fluid level. Furthermore, no fetal morphological abnormalities were found.

A multidisciplinary team involving cardiologists, anesthesiologists and obstetricians was created to coordinate the management of our patient´s pregnancy, delivery and postpartum period. Medical treatment was remained unchanged as the patient showed no evidence of arrhythmia throughout the rest of her pregnancy and in order to limit fetal risks. Due to the lack of information regarding to this condition in pregnancy and taking into consideration the patient´s individual high risk, a decision of a planned cesarean section at 37 weeks of gestation was made. There are no general recommendations of the management of patients with CPVT, and in this specific case, the patient suffered an ICD shock that led the team to add flecainide to the medication, so it was decided that once the fetal lung maturation was reached (around 37 weeks), it implied high risk to continue with the pregnancy.

However, unexpectedly, our patient was admitted to hospital at 31+0 weeks with premature labor and rupture of membranes. Only one dose of betamethasone was administered for fetal lung maturation. Anti-tachycardia therapies of her intravenous ICD were deactivated and adhesive defibrillation pads placed in the patient's chest before surgery. An emergency cesarean section and bilateral tubal ligation (following patient's demand and with prior informed consent) were then performed using combined epi-intradural anesthesia in L3–L4 level with 1.2 ml of bupivacaine 0.5% and 4 ml of lidocaine 2%. Clindamycin 600 mg and gentamicin 120 mg were also administered (due to allergy to beta-lactams) for antibiotic prophylaxis 30 minutes before the cesarean section. A healthy male with a birth weight of 1900 g was born. The 1-minute and 5-minute Apgar scores were 8 and 9, respectively. After the c-section, her anti-tachycardia therapies of her intravenous ICD were re-activated. As a personal decision, the patient declined breastfeeding. The postpartum period was uneventful although our patient suffered a new appropriate ICD shock after having been discharged requiring an increase on her flecainide dose (100 mg twice a day).

The newborn was admitted to the neonatal intensive care unit for 29 days due to prematurity. Respiratory support with CPAP was needed for 6 days due to mild

hyaline membrane syndrome. Cardiac monitoring during hospital admission showed no evidence of arrhythmia. He made good progress, was discharged and sent to home on a cardiac monitor and parents were educated in basic cardiopulmonary resuscitation. The baby has remained asymptomatic till date and in the follow-up, a sanger sequence analysis of the related gene study revealed that he is not a carrier of his maternal RYR2 variant.

Discussion

CPVT is a very rare disorder with a challenging diagnosis as VT episodes occur in the absence of structural heart disease or baseline electrocardiogram (ECG) abnormalities. Typical ECG during episodes reveals rapidly changing QRS complexes varying in amplitude, axis and duration (typically known as bidirectional VT).[2] It can present with recurrent syncope or even with sudden cardiac death, typically at the age of 7–12 years.

These VT episodes are typically related to adrenergic stimulation and can be triggered by emotional or physical stress which may be experienced in pregnancy.[1,2] In addition, CPVT is usually a lethal condition when untreated.[1,3] When talking about affected pregnant women, it is known that this condition can also carry adverse effects on the fetus, such as hemodynamic compromise of placental blood flow during maternal episodes of arrhythmia, teratogenic effects from maternal medication, inheritance of genetic susceptibility and possibly (but not very well known) adverse fetal effects due to ICD shock.[1] However, at present there is no evidence that puerperium implies an increased risk of VT recurrence in CPVT as it happens in other channelopathies such as some types of congenital long QT syndrome. Our data endorse this statement.

It is known that CPVT has a genetic basis typically involving four different genes: RYR2, KCNJ2, CASQ2 and ANK2.[2,4–6] An autosomal dominant form of CPVT was initially linked to chromosome 1q42-q43. One report suggested that abnormal RYR2 channels may account for at least one in every seven cases of sudden unexplained death.[4] However, RYR2 gene includes 105 protein-encoding exons and only some specific mutations are considered as pathogenic at the moment. More studies are required after sudden unexplained death to establish more pathogenic mutations of RYR2 and assess

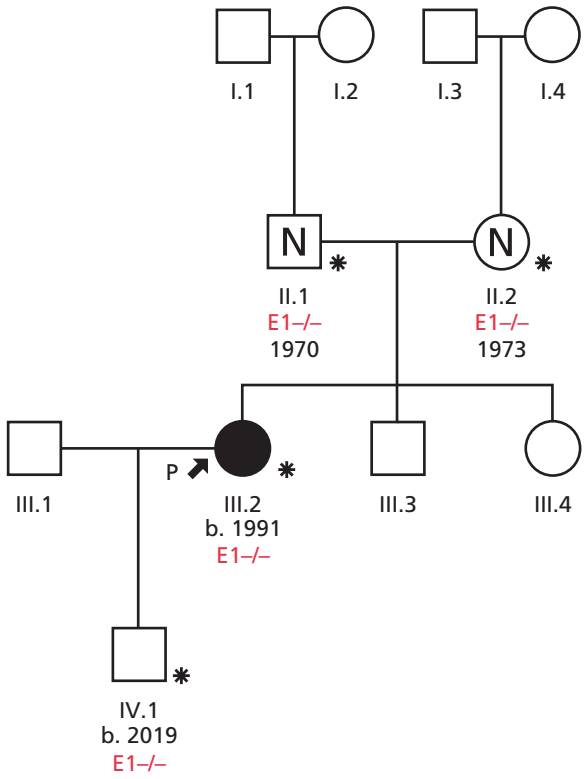

Fig. 1. Familiar pedigree.

the rest of family members. In this specific case, mutation was ruled out in both parents and a de novo presentation was confirmed in our patient. However, there is a lack of information at the moment for the typical inheritance of this specific gene mutation (**Fig. 1**).

Its treatment consists of avoidance of competitive sports, strenuous exercise and stressful events; medical therapy with betablocker (mainly nadolol) in combination with flecainide and left cardiac sympathectomy in case of recurrent episodes of syncope, high arrhythmia

burden or ICD shocks.[1] ICD implantation is becoming more and more controversial in this condition and needs a careful individual evaluation of its indication.

Betablockers are generally safe and effective during pregnancy, although fetal growth must be monitored due to the slight increased risk of fetal growth restriction. Beta-1 selective agents are the most used and recommended agents in pregnant women and atenolol should be avoided as it is clearly associated with fetal growth restriction.[7,8] Unfortunately, there is lack of information regarding antiarrhythmic use during pregnancy. In fact, although flecainide has shown to decrease arrhythmic events in patients who remain symptomatic despite betablocker,[8–15] there are major concerns about its use related to its potential effects on fetal growth, drug related side effects in the neonate and possible effects on uterine contractility. Lastly, ICDs are safe during pregnancy, and pregnancy has not been found to have any significant effect on ICD function.

We performed a review of the current literature regarding CVPT in pregnancy and we found 5 previously reported cases of pregnancies in women affected with this condition.[3,16–19] and a retrospective study.[20] including 96 patients with mild phenotype of CPVT. This retrospective study showed that most of the patients had an uneventful pregnancy and delivery; interestingly, only 14% of these patients were diagnosed before pregnancy (80% after it). This can represent a possible selection bias, including mostly mild or minimally symptomatic women. For that reason, although vaginal delivery has been described in some cases (only one of the 5 case reports (20%), not detailed in the retrospective study), we considered this information insufficient to systematically establish it as the preferred delivery route, especially in a severely symptomatic patients like ours.

A summary of the previously reported cases in the literature and their clinic and laboratory features are showed in **Table 1**.

Table 1. Literature review of PCVT and pregnancy.

	Chan and Dob[16]	Walker et al.[18]	Friday et al.[19]	Romagano et al.[3]	Ahmed and Phillips[17]
Age	27	19	19	27	17
Parity	G2C1	G1	G2A1	G2A1	G1
ICD	NO	NO	Yes	NO	Yes
Genetics	Not performed	Negative	Heterozygous RYR2 mut p.Leu470Pro	RYR2 Leu2426Phe	Not performed
Family history	Positive (uncle and 2 cousins)	Negative	Positive (mother)	Positive (sister)	Negative
Betablocker	Metoprolol 100 mg/12h	Bisoprolol 10 mg/12h	Propranolol 80 mg/12h	Nadolol 40 mg/24h	Atenolol 50 mg/12h
Antiarrhythmics	No	Flecainide	Propafenone 452 mg/12h	No	No
Events during pregnancy	No	Palpitations which lead to diagnosis	VT at 26 weeks for medication non-compliance	No	Multiple VT events reversed with IPC shock
Route of delivery	Scheduled c-section at 38 weeks	Scheduled c-section at 34 weeks	Spontaneous vaginal delivery at 30 weeks	Urgent c-section (after vaginal delivery attempt) at 40 weeks	Scheduled c-section
Anesthesia during delivery	Combined spinal-epidural	Not detailed	Early epidural	Epidural	Spinal
Infantile results	Not detailed	Not detailed	ICU admission due to distress. No arrhythmia documented. Negative genetics	No arrhythmia documented. Genetics positive for RYR2.	Uneventful. No arrhythmia documented. No genetics determined.
Mother's postpartum period	Uneventful	Uneventful	Uneventful	Uneventful	Uneventful

Conclusion

In this report, we describe a new likely pathogenic variant (p.Ser166Pro) in RYR2 causing a severe phenotype of CPVT in a pregnant woman. In spite of the challenging management of this condition during pregnancy and delivery, our patient had a successful outcome. This case illustrates the importance of a multidisciplinary approach in this clinical scenario and the benefits of an optimization of the medical treatment, and demonstrates that, even in severely affected patients, a successful pregnancy is possible under close control.

However, the risk of arrhythmic events and the course of pregnancy remain largely unknown in patients with CPVT, and further investigation is needed.

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