

Case of Fetal Cardiomyopathy Diagnosis and Brugada Syndrome

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Abstract: *Background:* Cardiomyopathies account for 8%-11% of the cardiovascular diagnoses detected in utero. *Case presentation:* We illustrate a case of fetal dilated cardiomyopathy (DCM) diagnosed in a woman arrived at our Emergency Room for reduced fetal movements at 35+3 weeks of gestation. The patient had an abnormal fetal echocardiography with evidence of enlarged fetal hearth with a cardiothoracic ratio over 95° p.le, a dilated left and right ventricle and a reduced wall contraction. The diagnosis was of DCM was done. A Cesarean section was performed at 36 weeks of gestation for pathological pattern of cardiotocography (CTG). The female newborn had normal post-natal adaptation. Heart ultrasound showed a severe biventricular DCM with poor kinesis and a Holter electrocardiogram (ECG) showed supraventricular isolated extra systoles. The newborn infant was treated with ACE inhibitor, beta blockers and diuretics with partial improvement and the DCM was confirmed by the referral center of Cardiology and cardio surgery. The panel of Next Generation Sequencing (NGS) for CM was performed. The sequence analysis identified the heterozygous c.554C>T variant in the SCN5A gene, which at protein level determines Ala185Val variant, that is described in the literature as associated with the Brugada Syndrome (BrS). This genomic variant was inherited by the mother. *Conclusion:* This article illustrates that when we have a fetus with DCM associated to demonstration of a genetic background, the counselling to the couple cannot exclude the presence of BrS in the child and an unknown genetic mutation in parents.

Keywords: Brugada syndrome, cardiomyopathies, dilated cardiomyopathy, hypertrophic cardiomyopathy, heart disease, mutation gene SCN5A, fetal ultrasound, alteration ECG, next generation sequencing, cardiac channelopathies.

1. INTRODUCTION

Cardiomyopathy (CM) are a various group of heart diseases that account for 8%-11% of the cardiovascular diagnoses detected in utero. There are two different types of fetal CM: dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) [1]. This is a case of fetal DCM, observed ultrasound examination during the pregnancy. The most common causes are: idiopathic in 44%, genetic-metabolic causes in 28%, inflammatory causes in 15% (Parvovirus B19 infection, Coxsackie virus, Epstein-Barr, adenovirus, HIV etc) and toxic causes (exposure to anthracycline during the chemotherapy) [2].

The most difficult part of examination is the counselling with the couple when CM was diagnosed in utero. One of the etiology of the CM is the genetic myocardial disease.

Several genes are potential implicated in the clinical phenotype of DCM. The combined use of linkage analysis and a large multi-gene disease-target panel based on next generation sequencing (NGS) technologies could aid in the identification of causative mutation. This case report analyzing a prenatal diagnosis of DCM confirmed by a cardiac ultrasound scan after birth where the SCN5A mutation gene was identified using a panel of NGS. This mutation was related with the Brugada Syndrome (BrS)

and clinical signs or alterations of ECG were present in the child. This report aims to argue the importance of counselling to the couple when a DCM was observed in prenatal ultrasound underlying the genetic disease etiology that can include possible cardiac channelopathies in the fetus.

2. CASE PRESENTATION

A pregnant woman, 35 years old at 35+5 weeks of gestation, arrived at our Emergency Room for reduced fetal movements. The patient was hospitalized for fetal wellbeing monitoring. She was a woman carrier of Huntington's Disease and the pregnancy was a result of in vitro fertilization (IVF). The patient was followed during pregnancy by a private clinic. Pre-implantation diagnosis and invasive prenatal diagnostic were carried out to look for the mutation of Huntington's disease. The result was negative. The patient referred a physiological pregnancy with some syncopal episodes.

The scan evaluation showed a regular anatomy of the fetus at 19th weeks of gestation. At 31th weeks of gestation the growth of the fetus was regular, but an holosystolic tricuspid valve failure was reported. The doctor of the private clinic suggested that the holosystolic tricuspid valve failure must be reassessed after the birth. No other controls

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was given to the patient to check the fetal heart.

After the hospitalization, the patient had a fetal echocardiography in our Prenatal Medicine Unit. An enlarged fetal heart was observed. Examination of the four-chamber plane, the great vessels and return of systemic and pulmonary veins usually does not reveal any major structural anomalies. The ventricles were both dilated (left and right), the ventricular wall contraction was reduced, the color Doppler shows the regurgitation of the mitral and tricuspid valves of the affected ventricles. All these data suggested a diagnosis of DCM.

The fetal cardiac frequency was 120-130 bpm. The following parameters were recorded: Cardiothoracic ratio (CT ratio) = 0,73 (50° p.le = 0,5 ; 97.5°p.le = 0,58); Heart Circumference = 166,2 mm (50°p.le = 146,73mm ; 97.5°p.le = 168,29 mm); Heart Area = 2216,1 mm² (50° p.le = 1349,41 mm² ; 97.5°p.le = 1664,5 mm²); Heart Width = 46,3 (50°p.le = 36,08 mm; 97.5°p.le = 40,77 mm); Heart Length = 51 mm (50°p.le = 46,83 mm; 97.5°p.le = 53,02 mm); Left Atrial Width = 16 mm (50°p.le = 13,67 mm; 97.5°p.le = 17,21 mm); Right Atrial Width = 21 mm (50°p.le = 14,82 mm; 97.5°p.le = 18,76 mm); Left Ventricular Width = 21,7 mm (50°p.le = 11,99 mm; 97.5° = 15,99 mm); Right Ventricular Width = 21,1 mm (50°p.le = 13,62 mm; 97.5°p.le = 17,78 mm); Left Ventricular/Right Ventricular Ratio = 1,02 (50°p.le = 0,89; 97.5°p.le = 1,18); Left Atrial Area = 290.5 mm²; Right Atrial Area = 200.7 mm²; Left Ventricular Area = 619.5 mm² [3]. A counseling was performed to the couple: DCM prognosis range from a good prognosis when the CM regresses pre or post-natally to very poor prognosis associated to fetal demise. The risk of in utero or neonatal death increase of presence the fetal hydrops, the stiff ventricular cardiac wall and the prematurity. Some fetus with CM may require cardiac transplantation post-natally. Some forms of idiopathic DCM can be associated with inherited diseases. The etiology was idiopathic in 44%, familial in 13%, inflammatory in 15% and genetic-metabolic in 28% [4].

Neonatal respiratory distress syndrome (RDS) prophylactic for the maturation of lungs has been recommended. Labor was pharmacologically induced for reduced fetal movements and not reassuring fetal heart monitoring related to DCM. The induction of labor was performed with a vaginal dose of Dinoprostone 2 mg and continuously monitoring by CTG. A Cesarean section was performed for pathological pattern of CTG.

The female newborn had normal post-natal adaptation: APGAR score was at 1st and 5th minute were 8 and 9 respectively. Weight was 2825 gr, Length 47 cm and head circumference 34.0 cm. At birth, the newborn

showed slight respiratory distress, for which she received on-invasive ventilator support (nCPAP) for the first three days of life. At birth transthoracic echocardiography was performed using EPIQ7 (Philips) with a S 12-4 MHz transducer. Echocardiogram showed a severe biventricular dilated cardiomyopathy with poor kinesis in absence of congenital malformations. Left (LV) and right ventricle (RV) dimensions were performed using a standard M-mode from a mean of both parasternal short and long axis view. All parameters were indexed for her body surface (BSA = 0.18 m²) [5]. The measures evaluated by echocardiogram were as follows: right ventricular end-diastolic dimension (RVEDD) 17 mm (mean 9.8 mm, range 6.6-14.6 mm, Z-Score 2.28); end-diastolic interventricular septum thickness (IVSd) 5.5 mm (mean 3.6 mm, range 2.5-5.1 mm, Z-Score 2.03); end-systolic interventricular septum thickness (IVSs) 6.8 mm (mean 4.7 mm, range 3.4-6.3 mm, Z-Score 2.05); left ventricular end-diastolic dimension (LVEDD) 22 mm (mean 17.6 mm, range 14.9-20.7 mm, Z-Score 2.25); left ventricular end-systolic dimension (LVESD) 17 mm (mean 10.9 mm, range 8.8-13.4 mm, Z-Score 3.53). The LV posterior wall thickness at end diastole and end systole were 3.5 mm and 5.8 mm respectively. The LV fractional shortening (SF) was 22.7 % and the LV ejection fraction (EF) calculated by the Teicholz M-mode method based on the data about the LVEDD and the LVESD obtained from the echocardiogram was 45%.

From the second week of life drug therapy for heart failure was started. At two months of life neonatal echocardiogram parameters were as follows: RVEDD 16 mm (mean 10.4 mm, range 7-15.4 mm, Z-Score 1.80); IVSd 5.4 mm (mean 3.7 mm, range 2.6-5.3 mm, Z-Score 1.76); IVSs 6.8 mm (mean 4.9 mm, range 3.6-6.6 mm, Z-Score 1.77); LVEDD 24 mm (mean 19 mm, range 16.1-22.5 mm, Z-Score 2.32); LVESD 16 mm (mean 11.8 mm, range 9.6-14.5 mm, Z-Score 2.42); LVPWd 3.8 mm (mean 2.9 mm, range 2.1-4 mm, Z-Score 1.36); LVPWs 6.5 mm (mean 5.6 mm, range 4.4-7.2 mm, Z-Score 0.99); SF 30% and EF 44%.

In the first days of life a Holter electrocardiogram (Holter-ECG) showed supraventricular isolated extra systoles. No other malformations or congenital anomalies were found with abdominal or cerebral ultrasound, fundus oculi and acoustic brain response was normal. Enterovirus and B19 Parvovirus PCR on plasma were negative. Metabolic examinations (blood spot lysosomal enzymes, blood spot alfa-glucosidases and alfa-galactosidases, urine organic acid, pyruvic dehydrogenase and respiratory chain enzymes on muscle biopsy) resulted all normal.



Figure 1: Fetal echocardiograms demonstrating the 4-chamber view in a case of DCM diagnosed at 35+4 weeks of gestation.

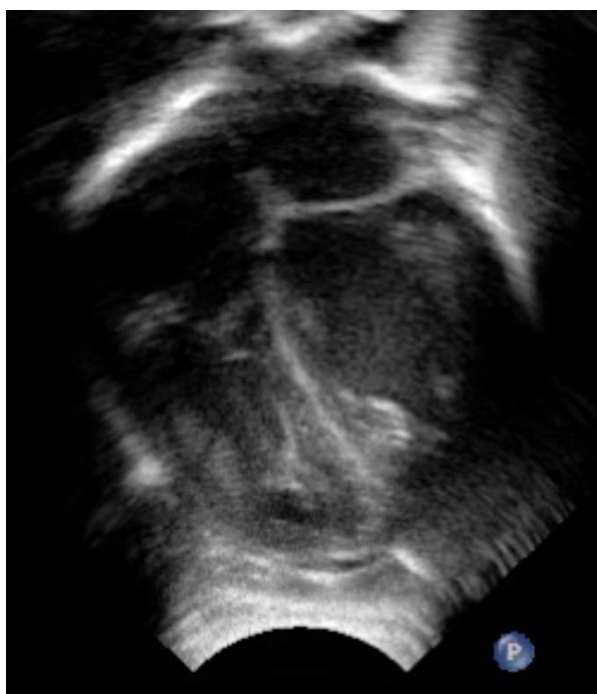


Figure 2: Apical 4 chambers view at two months of life.

The newborn infant was treated with ACE inhibitor, beta blockers and diuretics with partial improvement. She was discharged at one month old (3130 g). She was referred at regional center of Cardiology and cardio surgery where cardiomyopathy was confirmed. A watch and wait approach was recommended. NGS was taken and the mutation of the SCN5A was found. She continued therapy with ACE inhibitor, beta blockers and diuretics. The follow-up of the child with the pharmacological therapy at the first year of life, the clinical situation remained unchanged with the same dilated cardiomyopathy (DCM).

The growth was between 3rd -10th centile for length and weight. The panel of NGS for cardiomyopathy was performed. The analysis included coding regions and exon-intron junction of the following genes: ACTC1, ACTN2, BAG3, CAV3, CTNNA3, DES, DSC2, DSG2, DSP, FLNC, GLA, JUP, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYL2, MYL3, PKP2, PLN, PRKAG2, RBM20, TAZ, TCAP, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TTR, SCN5A, VCL.

Amplification and high-throughput sequencing was performed with seqCap EZ Custom Enrichment Kit (Roche Life Science), using Illumina sequencing platform (Next Seq 550). Analytical sensitivity and specificity was higher than > 99%. The sequence analysis identified the heterozygous c.554C> T variant in the SCN5A gene, which at protein level determines Ala185Val variant. This genomic variant was inherited by the mother.

The NM_198056.2 (SCN5A):c.554C>T (p.Ala185Val) is described in the literature as associated with the BrS [6,7].

After the genomic results, the mother had a cardiac examination: the ECG was regular, the morphometry of the heart was normal, dilated cardiomyopathy was not reported, no therapy was prescribed. Our cardiologists did not perform the drug challenge test because the additional diagnostic value is not clear and considered to be limited and the test is not without risk for provoking arrhythmic events in a patient with regular have been screened for CM with the NGS panel and in both was found the only mutation of SCN5A.

3. DISCUSSION

The frequency of CM in the fetal life is difficult to be determinate: CM occurs in about 2-7% of babies, but probably the frequency during the fetal life is higher. CM account for 8%-11% of the cardiovascular diagnoses detected in utero [1].

There are two types of fetal CM: dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM). DCM is characterized by cardiac dysfunction, which can be univentricular or biventricular, systolic dysfunction with/without chamber enlargement but without increased wall thickness. HCM is diagnosed when the ventricular wall thickness is >2SD above the mean for gestational age compared with previously published normal data, with/without ventricular systolic or diastolic dysfunction [8].

The most common causes are: idiopathic in 44%, genetic-metabolic causes in 28%, inflammatory causes in 15% (Parvovirus B19 infection, coxsackie virus, Epstein-Barr, adenovirus, HIV etc) and toxic causes (exposure to anthracycline during the chemotherapy) [2].

One of the etiology of the CM is the genetic myocardial disease. Several genes are potential implicated in the clinical phenotype of DCM. The combined use of linkage analysis and a large multi-gene disease-target panel based on next generation sequencing (NGS) technologies could aid in the identification of causative mutation [9].

At present, knowledge of a specific mutation may not provide guidance in formulating a diagnosis or determining a prognosis. Genetic testing is recommended, however, to support the clinical diagnosis, for early detection of relatives at potential risk, and to advance through research our understanding of the genotype–phenotype relationship [10].

Different causative genes mutation is related with pediatric CM. There are multiple modes of inheritance for CM including autosomal dominant, autosomal recessive, X-linked and mitochondrial. Isolated, autosomal dominant CM is the most common genetic form of CM among individuals of all ages. There are shared genetic causes in children and adults [11,12], especially in families with autosomal-dominant CM. Variants can be inherited or occurred the novo [13,14].

The SCN5A mutation gene have been described in different types of CM. This human gene SCN5A encodes the abnormalities in the sodium channel current in the cardiac cell which is the genetic basis of BrS channelopathies [15].

BrS was described as a clinical entity and it is characterized by the presence of typical electrocardiographic (ECG) pattern and associated with a risk of sudden cardiac death (SCD) [16]. BrS is diagnosed when one of the following criteria occurs: A) Family history: SCD in a family member < 45 years or ECG type 1; B) Arrhythmia-related symptoms: syncope, seizures, or nocturnal agonal respiration; C) Ventricular arrhythmias: Polymorphic ventricular tachycardia or Ventricular Fibrillation [17].

Inheritance of BrS occurs via an autosomal dominant mode of transmission. The first and only gene to be linked to BrS is SCN5A, the gene that encodes for the subunit of the cardiac sodium channel gene. About 2 dozen of these mutations 73 have been studied in expression systems and shown to result in loss of function because of failure of the sodium channel to express. SCN5A mutations account for ~ 18% to 30% of BrS cases. A higher incidence of SCN5A mutations has been reported in familial than in sporadic cases [10].

The genetic basis of BrS are based on an anomaly of the Na⁺ channel in the cardio myocytes. SCN5A encodes the main Na⁺ channel, an integral membrane protein found primarily in the cardiac muscles. This protein mediates the influx of Na⁺ through the cells, thus generating an initial upstroke of the cardiac action potential. Voltage-gated Na⁺ channels are responsible for the generation and propagation of the action potential in different excitable tissues. Mutations of SCN5A can cause arrhythmogenic cardiac syndromes including BrS and long-QT syndrome [18].

It has been demonstrated that the clinical manifestations associated to the mutation of SCN5A do not exclusively include electrical disorders but also several CM [19].

Genetic variations in the SCN5A gene that resulted in electrical and structural cardiac remodeling were first described in 2003 by Groenewegen et al. in a large family with atrial standstill, a rare form of atrial cardiomyopathy [20]. At the same time, it was shown that the clinical spectrum of rare SCN5A genetic variants could be expanded to arrhythmogenic right ventricular cardiomyopathy (ARVC) and DCM accompanied by arrhythmias and conduction disorders [21,22].

There is an unbiased link between mutations in the SCN5A gene and CM. Mutations can cause arrhythmias and chamber dilation, but additional genetic factors may also be involved in cardiac remodeling. The NGS technologies hope to provide insights into molecular pathways and genotype–phenotype correlations. The

altered Na⁺ channel increases electrical heterogeneity in the myocardium and causes arrhythmias. Several studies focused on detailed clinical phenotyping and the assessment of treatment efficacy might provide a clue to effective strategies for personalized therapy [19].

Currently, twenty-four mutations in the SCN5A gene leading to the development of different types of cardiomyopathy have been described, and most of them (16 variants) were found in DCM patients in at least one observation [10]. These observations of structural changes of the myocardium in SCN5A-positive patients may reveal a combined manifestation of two diseases: cardiac arrhythmia resulting from an SCN5A mutation and cardiomyopathy of primary or secondary origin, suggesting a more complex genetic background. In most studies extensive genetic screening for panels of genes responsible for the “cardiomyopathy of interest” was not performed for SCN5A-positive patients [18].

In our case, the diagnosis of fetal DCM was discovered at 35+3 gestational weeks. When a DCM is suspected, the big challenge is to find out the underlying cause. A detailed ultrasound examination of the fetus is recommended, combined with Doppler investigation of the fetal arteries and precordial veins. The etiology of the DCM can be various: idiopathic in 44%, genetic-metabolic causes in 28%, inflammatory causes in 15% and toxic causes. Also the prognosis can be variable and include intrauterine fetal demise, sudden death infant syndrome e heart transplantation. The mother and the baby have been screened for CM with the NGS panel and in both was found the only mutation of SCN5A. The NM_198056.2 (SCN5A):c.554C>T (p.Ala185Val) is described in the literature as associated with the BrS.

Therefore in our newborn patient, affected by fetal onset DCM, we have found the NM_198056.2 (SCN5A):c.554C>T (p.Ala185Val) mutation, that is described in the literature as associated with the BrS and/or DCM. This mutation was inherited by the mother, who at the age of 37 didn't show symptoms of BrS and/or DCM. This does not mean that the woman is unaffected, but it means that at the moment she is phenotypically negative, a part of syncopes.

The syncopal episodes during the pregnancy is considered a marker of risk for the development of ventricular arrhythmias in patients with BrS, but it is not associated to worse outcome during the peri- and postpartum periods or during the follow up [17].

We cannot exclude that she will manifest symptoms later in life. Moreover, in the context of SCNA mutation, an extreme variability of clinical expression is well known.

Consequently, the peculiarity of our report is the early clinical expression of DCM (fetal onset) in association with (SCN5A): c.554C>T mutation.

The lack of segregation (carrier mother still not affected or mildly affected because of syncope) does not exclude a causative role of the (SCN5A): c.554C>T mutation in the fetal-neonatal DCM. As the big challenge is to found the underlying etiology of fetal CM, the description of a new case of fetal-neonatal onset DCM associate with SCN5A mutation contributes to further delineate the spectrum of fetal DCM and to improve prenatal and postnatal counselling.

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