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Case Report

Fetal Dilated Myocardiopathy – Case Report: Association with a heterozygous mutation in *MYH7* Gene

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Abstract: We report a case of dilated myocardiopathy with ascites and cardiac dysfunction detected at 20 weeks' gestation. Baby was born at 33 weeks and 6 days, weighing 2530g, delivered by cesarean section and admitted to NICU. Postnatal echocardiography confirmed biventricular severe dysfunction, need of ventilatory support, vasoactive drugs, and prostaglandins. He was investigated for metabolic, infectious, and viral diseases with no positive results. After 6 weeks, he was transferred to a transplant center. Exome sequence showed a heterozygous mutation in the *MYH7* gene (OMIN-160760.0028).

Keywords: Cardiac failure; Dilated myocardiopathy; *MYH7* gene.

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1. Introduction

Fetal Dilated cardiomyopathy (DCM) is an infrequent disorder and accounts for a small proportion of cardiac abnormalities observed during fetal life [1]. Most cardiomyopathies recognized in utero are associated with dilated, poorly contractile left ventricles. DCM may be the result of a number of different disease processes including viral infections, metabolic disease, fetal anemia and fetal tachycardias [2].

The myosin heavy chain 7 (*MYH7*) gene encode for B-myosin, a key component of the cardiac sarcomere, and some pathogenic variants of this gene, may be associated with myocardial contractile abnormalities and dilated cardiomyopathies. Pathogenic variants in *MYH7* have been described in 1 to 5% of DCM cases [3].

Several publications have described the possible association of cardiomyopathies to mutations in the *MYH7* gene. Catrina et al described 3 different phenotypes associated with this gene including a dilated form of cardiomyopathy [3, 4]. The annual incidence of cardiomyopathies in childhood is around 1.2 for each 100.000 children. More than 40 per cent of affected children ultimately die or require cardiac transplantation [3].

2. Case Report

A 33-year-old primiparous Brazilian woman who had an uneventful antenatal course until 34 weeks of gestation. She was referred to our tertiary center due to diagnosis of dilated myocardiopathy with ascites and cardiac dysfunction detected at fetal ultrasonography. There was no previous family history of cardiac disease. A male neonate weighing

2530g was delivered by C- section with Apgar scores of 8 at 1 min, and 9 at 5 minutes. The baby was electively intubated in the delivery room and transferred to NICU.

Mechanical ventilation with support parameters was initiated, as well as adrenaline and milrinone infusions. First echocardiography showed severe biventricular dysfunction, moderate to severe tricuspid regurgitation, mild mitral regurgitation, and patent ductus arteriosus with L-R shunt. Laboratory tests were negative for viral and bacterial diseases and metabolic screening (Tandem Mass Spectrometry) was also negative. In the tenth day, baby presented a positive urine culture and was started on antibiotics. A trial with 3 doses of Levozimedan was attempted with 11 days of age with small improvements in cardiac function.

With 12 days, he was extubated for nasal CPAP. A genetic consult indicated a karyotype and DNA extraction, looking for markers of a genetic disorder. A cardiac magnetic resonance showed a biventricular systolic dysfunction (FE LV 12% e RV 22%) without myocardic necrosis or fibrosis and no evidence of metabolic disease. At 16 days of life, cardiorespiratory condition deteriorated, and baby was re-intubated. Echocardiography still showing an important mitral, tricuspid, and pulmonary regurgitation with PAP 70-75%. Baby was started on furosemide. At 19 days, a new cycle of Levozimedan was initiated. At the 25th day echocardiography showed the same findings of severe myocardic dysfunction (FE 17 a 20%) (Figure 1)

At 30 days, baby was a transfused for anemia and started on antibiotics because of another positive urine culture. Clexane was started for the possibility of intramural cardiac thrombosis. Results of new generation genome sequency identified a heterozygous mutation in the *MYH7* gene (OMIN-160760.0028). Both parents tested negative for the mutation. This analysis was performed with an Illumina sequencer, with reference to the GRCh38 genome version, with processing of the BAN files aligned by the Exome Depth program (https://cran.rproject.org/web/packages/ExomeDepth/index.html), and allele frequency analysis by GnomAD. They also report that the sequencing resulted in a percentage of target bases with at least 10 readings: 99.9%, Average number of times each database was read: 82 and Number of sequences generated: 34,426,793. The name of the variant is Chr14:23.432.666 C>T T (or alternatively c.475G>A - ENST00000355349), which results in a missense mutation with the exchange of the amino acid aspartate at codon 159 for an asparagine (p. Asp159Asn).

As clinical condition was worsening, with no significant improvement in cardiac function and moderate response to several attempted medications, family agreed to transfer the baby to a transplant center and offer a possible therapeutic option. In the subsequent weeks, baby progressively stabilized and was discharged home. Baby is now two years of age, has been submitted to heart transplantation and is at home, in a stable clinical condition.

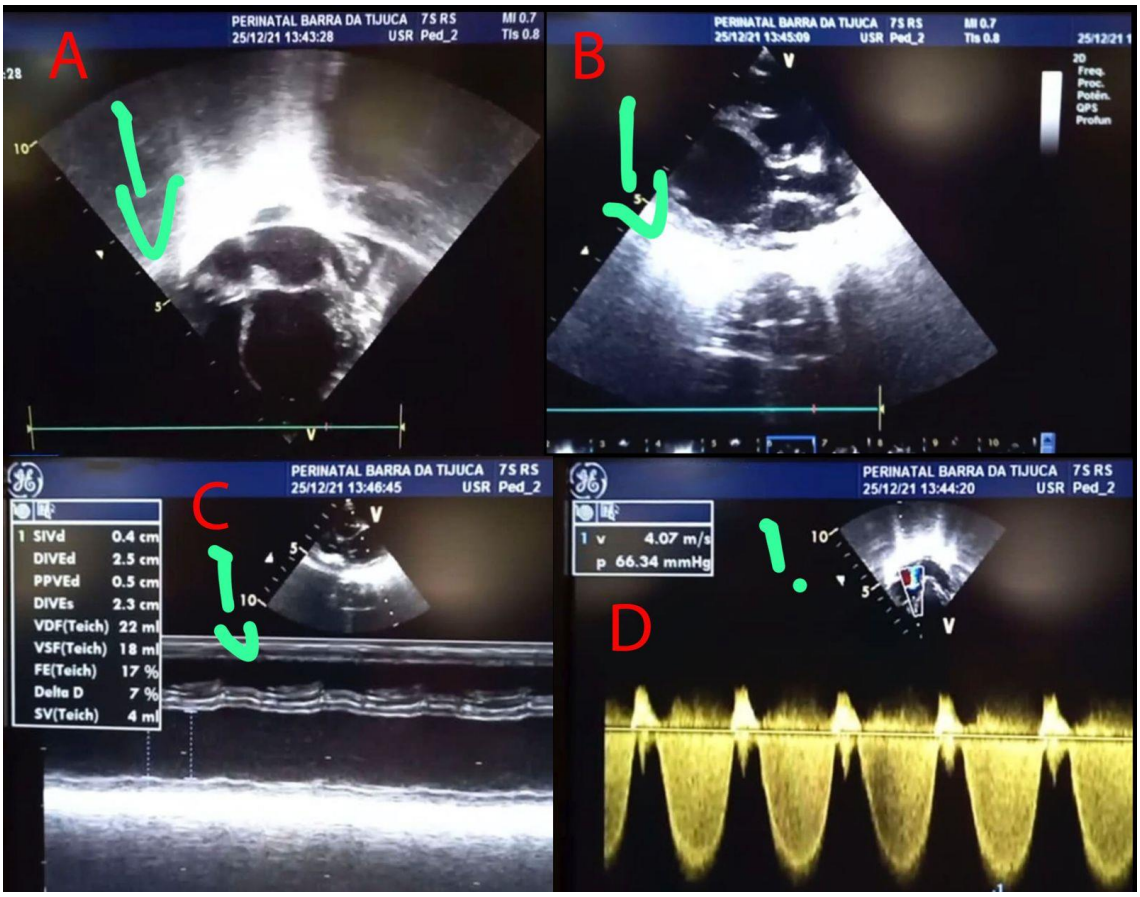
3. Discussion and conclusions

We describe a case of Dilated Cardiomyopathy, possibly associated to *MHY7* gene. Fetal evaluation showed ascites and cardiac disfunction at 20 weeks gestation. After birth, baby showed signs of heart failure, with biventricular dysfunction and very low ejection fractions. The possibility of infectious diseases was excluded by diagnostic tests and the genetic evaluation showed a heterozygous mutation in the *MYH7* gene. The myosin heavy chain (*MYH*) genes are a family of genes that encode for proteins that are involved in muscle contraction. Defects or mutations in these genes can lead to a variety of muscle-related disorders [3]. There are several different *MYH* genes, each of which is associated with a different type of muscle tissue. *MHY7* is primarily expressed in cardiac muscle, and mutation in these gene has been associated with several cardiac conditions, including hypertrophic cardiomyopathy, dilated cardiomyopathy and left ventricular noncompaction.

Several reports have associated cardiomyopathies with this mutation. Kamisago et al [5, 6] describe a family with dilated cardiomyopathy with a mutation in beta-myosin

heavy chain gene, where one member had received cardiac transplant at 23 years of age and a female child developed congestive heart failure at 2 years of age. In other report, another family with *MYH* mutation where the father was given the diagnosis of cardiomyopathy at 11 years of age and a daughter died suddenly at the age of 2 months. A 4-year-old daughter, diagnosed with dilated cardiomyopathy at the time of birth, was found to have fetal left ventricular dilatation.

Figure 1. A. Apical Four Chamber View showing marked enlargement of all cardiac chambers mainly of left ventricle. **B.** Longa Axis Parasternal View showing marked enlarged left ventricle. **C.** Ejection Fraction severely compromised (17%). **D.** Severe Mitral Regurgitation due to ventricle dilatation.



In a series of 46 young patients with dilated cardiomyopathy Beecroft et al. identified 2 mutations in the *MYH7* gene. One patient with this mutation was 35 years old when diagnosed with dilated cardiomyopathy and the other was 18 years old when diagnosed with dilated cardiomyopathy [7]. The *MYH7* gene encodes the beta-cardiac/slow skeletal myosin heavy chain (MYHC-slow), expressed predominantly in the cardiac ventricles and slow skeletal (type 1) myofibers. Myosin acts as a molecular motor through its interaction with actin of the thin filament, which is vital for skeletal muscle force generation [4].

In 2020, Kuo et al described in a case report a Fetal Dilated Cardiomyopathy associated with variants of uncertain significance in *MYH7* and *DSG2* genes. Diagnosis was made at 31 weeks of age several weeks after a maternal flu-like disease. Although maternal Coxsackie virus titers were elevated post-natal cord blood was negative. Genetic testing for DCM demonstrated heterozygous variants of uncertain significance in the *MYH7* and *DSG2* genes, exactly as our case. Baby required temporary inotropic support but at the age of two years an echocardiogram showed normal biventricular function [8].

Dilated cardiomyopathy diagnosed in fetal life can be a consequence of variety of conditions, including, infectious, metabolic, renal, and genetic diseases [8-11]. Transition from fetal life is characterized by important hemodynamic changes particularly in infants with DCM, who will require NICU admission for stabilization and proper diagnosis. Our patient was non-responsive to inotropic drugs but remained hemodynamically stable using diuretics during the neonatal period even with a veery compromised cardiac function.

We report a very severe case of DCM, not associated with metabolic, infectious, or renal diseases, who required several weeks of newborn intensive care, with a very low ejection fraction and critical condition. Genetic testing showed a heterozygous mutation in the *MYH7* gene, initially thought as of uncertain significance, but probably pathogenic, with both parents testing negative for this mutation and no family reported cases of DCM. Our report may add some evidence of the association of DCM with *MYH7* mutation.

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Research Ethics Committee Approval: Information about baby's clinical condition as well as the results of tests can be accessed through the medical records of the Perinatal Maternity Hospital (Rio de Janeiro) and Israelita Albert Einstein Hospital (São Paulo), where he underwent clinical treatment and heart transplant.

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Conflicts of Interest: None.

Supplementary Materials: None.

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