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Case Report

Novel Bi-Allelic Mutations in the RPL3L Gene Causing Severe Neonatal Dilated Cardiomyopathy

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Abstract

Dilated cardiomyopathy (DCM) in neonates is a rare condition with a broad differential diagnosis, including genetic etiologies. Familial forms of DCM are genetically heterogeneous, recent studies have implicated variants in RPL3L gene, encoding a ribosomal protein, in severe neonatal DCM. We report a case of fulminant heart failure with rapidly progressive neonatal dilated cardiomyopathy and multimodal support, associated with bi-allelic RPL3L variants.

Keywords: *Dilated Cardiomyopathy; RPL3L Gene; Genetic Testing; Neonatal Heart Failure; Heart Transplantation*

Abbreviations

DCM: Dilated Cardiomyopathy; RPL3L: Ribosomal Protein Large 3-Like; NICU: Neonatal Intensive Care Unit; ECMO: Extracorporeal Membrane Oxygenation

Introduction

Neonatal cardiomyopathies are rare diseases of the heart muscle associated with cardiac dysfunction. There are different presentations such as hypertrophic, dilated or restrictive forms, as well as, noncompaction and arrhythmogenic right ventricular cardiomyopathies [1]. Dilated cardiomyopathy (DCM) is characterized by cardiac dilatation and reduced systolic function. Neonatal onset of DCM can have a rapid progression to cardiac decompensation and death unless the patient undergoes heart transplantation. Its etiology may be acquired or inherited. Myocarditis is responsible for the majority of cases of acquired dilated cardiomyopathy, but it can be a consequence of different pathologies (ischemia, arrythmias, endocrine, metabolic, systemic, autoimmune disorders, toxic…), so differential diagnosis is quite broad [2]. Genetic forms of DCM include different modes of inheritance, autosomal dominant, autosomal recessive, X-linked and mitochondrial pattern [3]. Most mutations are in genes encoding components of the sarcomere, the Z-disc and the desmosome. But recent studies have implicated a novel mutation in the ribosomal protein large 3-like (RPL3L) gene [4]. RPL3L genes encode the 60S ribosomal protein, which

is specifically expressed in cardiac and skeletal muscle [5]. RPL3L pathologic variants are associated with rapidly progressive neonatal DCM and heart failure with a poor prognosis [6].

Case Report

A previously healthy full term 15-day-old male neonate with an unremarkable antenatal and perinatal history (non-consanguineous family with healthy parents, originated from Colombia), was admitted to our hospital for feeding difficulty, irritability without fever, in the last two days. Examination revealed, tachycardia, tachypnea and irritability. Blood workup showed lactic acidosis (8.1 mmol/l), high heart failure biomarker levels (Troponin I 370 ng/ml, NT-ProBNP 63.642 pg/ml), the rest of laboratory tests were normal and inconclusive for infection and metabolic disease. His electrocardiogram showed sinus tachycardia, with biatrial enlargement and nonspecific repolarization abnormalities. Echocardiogram showed a normal structural heart but with a marked left ventricular dilatation (25 mm, Z-score +2.2), depressed fractional shortening 18% and mild mitral regurgitation (Figure 1). Patient was admitted in NICU for further management. Despite intensive medical therapy, including inotropes (adrenaline, milrinone, levosimendan) and immunoglobulin, the patient required extracorporeal membrane oxygenation (ECMO) support on the day 14 of illness. Subsequent interventions included atrial septal stenting and implantation of a left ventricular assist device (Berlin Heart Excor®). On the day 24, the patient underwent orthotopic heart transplantation (Figure 2), but developed primary graft failure necessitating continued ECMO support. Unfortunately, after multiple complications (alveolar haemorrhage, renal failure, bacterial sepsis) the patient died at the age of 2 months and 23 days of age. Genetic analysis revealed two heterozygous variants in RPL3L gene, c.922G>A, (p.Asp308Asn) inherited from his mother, and c.76C>T (p.Arg26Trp) inherited from his father, both asymptomatic.

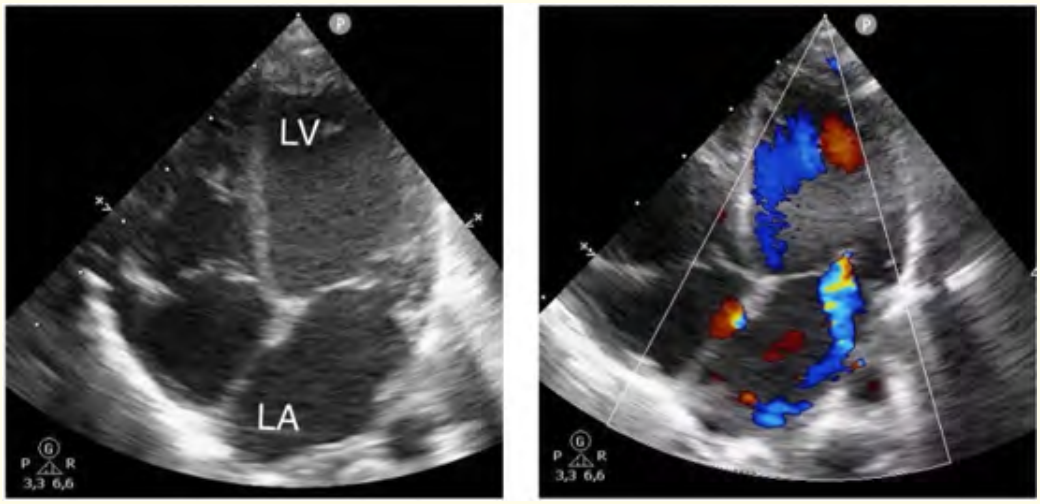

Figure 1: *2D echocardiography. Apical four-chamber view.*

Enlargement of the left atrium and left ventricle. Color-flow Doppler shows a mitral insufficiency and foramen ovale

(shunt left-right). LV: Left Ventricule; LA: Left Atrium.

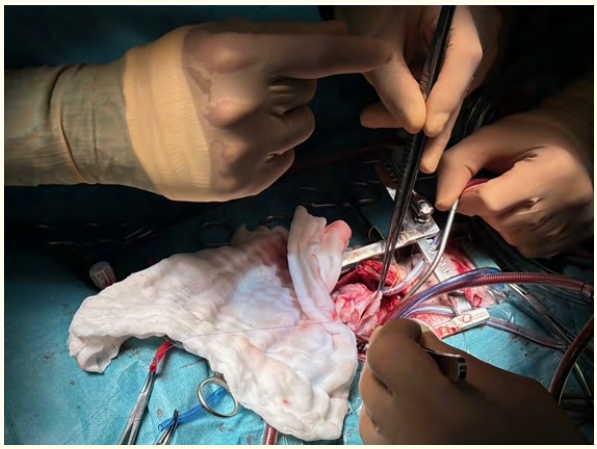

Figure 2: *Orthotopic heart transplantation.*

Discussion

This case underscores the importance of considering genetic causes in neonatal DCM and highlights the potential role of RPL3L variants [6]. The RPL3L gene plays a role in cardiomyocytes growth and function. The involvement of ribosomal factors in the pathogenesis of dilated cardiomyopathy possibly reveals a novel disease-associated mechanism [4]. Bi-allelic missense variants in RPL3L caused a severe dilated cardiomyopathy on neonatal period, in our patient, despite multimodal support, the fulminant heart failure could not be prevented. Early genetic diagnosis can inform management decisions and family counselling, specially when a genetic diagnosis has a known fatal outcome [5].

Conclusion

RPL3L is a newer and likely pathogenic gene associated with a severe form of early-onset dilated cardiomyopathy with poor prognosis necessitating heart transplantation, but further research is needed to elucidate the pathogenic mechanisms of RPL3L-related cardiomyopathy.

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Conflict of Interest

The authors declare no conflicts of interest.

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