Troponin T mutation as a cause of left ventricular systolic dysfunction in a young patient with previous surgical correction of aortic coarctation

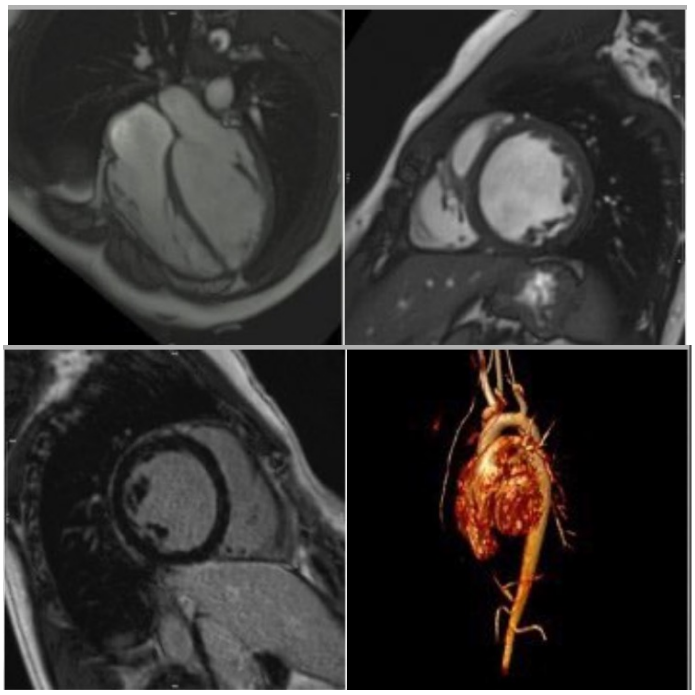

Figure 1. 1,5 Tesla cardiac magnetic resonance (CMR) showing a moderately dilated, hypokinetic left ventricle at 4 chamber (a) and midventricular short-axis view (b). Figure 1c shows post contrast short axis view excluding late gadolinium enhancement (LGE). Figure 1d three-dimensional reconstruction of aortic arch where no signs of recoarctation were detected.

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With an estimated prevalence of 1 in 2500 live births, Coarctation of Aorta (COA) is a major cause of morbidity and mortality among adults with congenital heart disease (ACHD). Lifelong surveillance after surgical correction is mandatory, as increased risk of cardiovascular events is well documented, particularly after the third decade of life including systemic hypertension, aortic valve abnormalities, and risk of aortic aneurysm . Although it has been widely accepted that increased left ventricle (LV) afterload plays a major role in cardiovascular events, to date there is a lack of data about the association of COA and left ventricular systolic dysfunction (LVSD). Few cases of LVSD have been reported in literature and mostly, recoarctation has been considered causative, as hemodynamic relief is associated to complete regression of LVSD.
Herein we report the case of a 19 y.o boy who was referred to our clinic because of unexplained LVSD and positive family history of dilated cardiomyopathy (DCM).

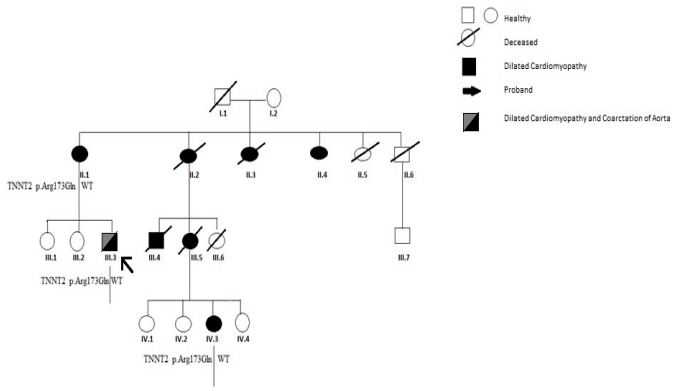

Figure 2. Family pedigree of the proband.

Case Presentation

The proband is the third son of non-consanguineous parents. At the age of 19 y.o he was referred to our clinic for a comprehensive evaluation after he experienced mild exertional dyspnea in the last few weeks. Family history was positive to sudden death (his cousin died cousin aged 3months) and to DCMP and heart transplant (HT): a maternal aunt and her son who then died at 42 and 24 y.o. respectively. Figure 2 summarizes family pedigree.
At birth, he was diagnosed with COA and therefore surgically corrected by end-to-end anastomosis and patch aortoplasty. Since then, he had been routinely evaluated at Pediatric Cardiology Unit in our Hospital clinic with serial clinical and echocardiographic evaluations. He had normal growth parameters (weight 85 Kg and height 165 cm) and reached regularly developmental milestones suggesting an isolated form of COA. During routine evaluation, the patient complained progressive exertional dyspnea, NYHA II-III. There was no medical history for recent infectious nor inflammatory events. On physical examination: lower limb pulses were bilaterally palpable, there was no significant upper and lower limbs pressure differences and there were no signs of peripheral congestion (neither crepitation nor hepatomegaly). Echocardiographic examination showed a mildly reduced left ventricular ejection fraction (LVEF) (~42%) with nondilated LV. Residual isthmic gradient was not significant (<20 mmHg) and absence of holodiastolic run off was ascertained. Echocardiography excluded other findings that may suggest haemodynamic consequences. Aortic valve was tricuspid and no mitral valve abnormalities were found. Ambulatory blood pressure monitoring excluded hypertensive status suggesting recoarctation. Complete blood count, thyroid hormones, serum electrolytes, lipid profile, hepatic function, serum creatinine and NT pro BNP laboratory values were within the reference ranges. Medical therapy was introduced and well tolerated with beta-blocker (Bisoprolol) and ACE inhibitor (Ramipril).
The patient was referred to Inherited and Rare Diseases Unit in the suspicion of an underlying cardiomyopathy. For the purpose of tissue characterization, a cardiac magnetic resonance (CMR) was performed showing a moderately dilated, hypokinetic left ventricle (LV), with mildly reduced EF (45%). No evidence of early and late gadolinium enhancement (LGE) was detected and residual isthmic coarctation was excluded (Figure 1). Based on the clinical presentation and family history, genetic counselling was performed and molecular testing was suggested. According to the dispositions of local ethics committee, informed consent was appropriately obtained for genetic investigations through next generation sequencing (NGS) with a panel of 111 genes, known to be associated with cardiomyopathies.
A blood sample in EDTA was collected from the subject. Genetic testing identified a heterozygous variant in TNNT2 (NM_001001430.2): c.518G>A (p.Arg173Gln). According to American College of Medical Genetics (ACMG), the variant is classified as pathogenic / likely pathogenic (class 5-4) which confirms the clinical suspicion of Cardiomyopathy. The NGS variant was also validated by Sanger sequencing. The variant is previously reported in literature and is associated to the phenotype of cardiomyopathies[7]
Thus, the relatives were invited to join the cascade program including both phenotyping (cardiac screening) and genotyping (analysis of the pathogenic variant identified in the proband).
Cascade family screening revealed TNNT2 variant in the mother (II.1) and his cousin (IV.3). Both of them were phenotype positive (affected by DCM) at cardiac screening at out Hospital clinic. The two sisters of the proband were unavailable to screening. Figure 1 reports both phenotyping and genotyping of the reported family.
To date, the association of dilated cardiomyopathy and repaired COA is very rare. LVSD has been commonly associated to recoarctation in infancy, nonetheless heart failure symptoms seem to regress after hemodynamic relief of aortic gradients. Potential pathophysiologic mechanism of progression to DCM in severe COA in infancy seems to occur after closure of arterial duct, because formation of an adequate collateral circulation is not allowed promptly. Mechanical wall stress imposed by hemodynamic overload in COA may trigger left ventricular hypertrophy (LVH) and concentric remodeling. Different pathways seem to be involved in adaptive LVH, including increased transcription of sarcomeric proteins, release and production of cytokines and growth factors and production of neurohormonal mediators that contribute to the increase in myocardial mass. Nonetheless, the burden of chronic pressure overload may trigger the compensatory hypertrophy to evolve to maladaptive hypertrophy with cardiac dilatation and loss of systolic function. Isthmic recoarctation should be included in the differential diagnosis of children and infants with DCM regardless of previous surgical or percutaneous correction, and aortic imaging using CMR or CTA is recommended by current Guidelines; nonetheless this was ruled out in our case.
This case highlights the role of careful history taking: a family history of cardiomyopathy should not be overlooked even when the clinical setting seem to suggest a predisposition to hemodynamic factors for LVSD