RESEARCH ARTICLE

A CASE OF RARE INHERITED RESTRICTIVE CARDIOMYOPATHY CAUSED BY A NOVEL MUTATION IN MYH7 GENE

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Manuscript Info

Abstract

Introduction: Inherited restrictive cardiomyopathy (RCM) is a rare cause of RCM associated with cytoskeletal and sarcoma gene mutations. We describe a case of inherited RCM due to MYH7’s genetic mutation. Case description: A 66 year-old-woman was admitted for acute global heart failure. She had a family history of RCM with a mutation of MYH7 gene: son’s sudden death at 30, one of her daughters who is 40 and grandson who is 1. The transthoracic cardiac ultrasound (TTE) showed a bi-atrial dilation, a non-dilated left ventricle (LV) non-hypertrophied. Genetic investigation found the same pathogenic missense mutation (c. 1477A>G in heterozygous state) in our patient and her daughter who has a non-obstructive hypertrophy cardiomyopathy (HCM). A few weeks later, our patient had a syncope on complete atrioventricular block. A triple chamber pace maker was installed.

Discussion: Familial RCMs’ mutations are characterized by high allelic, genetic and phenotypic variability, with autosomal dominant inheritance and variable penetrance. This mutation is rarely found in RCM, it is usually reported in HCM (OMIM 160760). Genetic screening should be considered to identify patients at risk in families with suspected familial transmission. MYH7 mutations seem to be associated with severe phenotypes, earlier age of onset and more pejorative evolution than other mutations.

Conclusion: The evaluation of familial RCM requires an understanding of its variable phenotypic expression and incomplete penetrance. RCM and HCM may coexist in the same family. Genetic testing for hereditary RCM should be considered when secondary causes have been excluded.

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Introduction:- The restrictive cardiomyopathy (RCM) is the least common cardiomyopathy (CM) representing less than 5% of cases, its prevalence is estimated at 0.003%. (Richard, 2016). Its incidence rate is 0.06 for 100 000 person-year. (Langlard, 2004) This condition is characterized by an anomaly of the diastolic function of one or two ventricles, (Huang & Du, 2004) with a reduction of the volume and stiffness of the muscle walls of the ventricles. The systolic function is maintained to a certain degree. (Hughes and McKenna, 2005). The RCM is in most cases secondary to...
another infiltrative pathology (amyloidosis, endomyocardial fibrosis). It can be linked to family history (10% of cases) or genetic predisposition (30%) (Shah & al, 2017).

The case presented is an observation of a familial RCM with a genetic mutation of MYH7.

Materials and Methods:-
This study is based on a case study of a 66-year-old woman who presented with 3 months of progressive dyspnea on exertion and volume overload. Clinical presenting complaints and progression of symptoms, physical examination, laboratory and radiographic investigations, and genetic study were all given special attention during the review of these patient records.

Case Presentation
A 66-year-old woman who presented to our emergency with 3 months of progressive dyspnea on exertion and volume overload. She was admitted for acute global heart failure.

The patient presented with a newly diagnosed diabetes, in addition to her age and menopause as cardiovascular risk factor.

The patient had a family history of sudden death of her son at 30 during a physical exercise, of which the autopsy revealed the existence of an RCM linked to a genetic mutation of the MYH7 gene. The same mutation was found in one of her daughters who is 40 and grandson who is 1.

Upon her admission, the clinical exam results showed signs of orthopnea. Her blood pressure was at 100/60 mmHg, hearth rate at 137 beats/min, oxygen saturation was 96% at ambient air. There were signs of global heart failure with a left galloping sound, cracking rales at the bases, hepatomegaly and lower limbs edema.

The electrocardiogram showed low voltage, a typical atrial flutter at variable conduction with a ventricular rate of 125 beats/min, and a complete left bundle branch block (Figure 1).

Chest X-ray showed a triangular cardiomegaly in connection with dilation of the atria and a peri-hilar vascular overload (Figure 2).

Biology found BNP at 1000.70 pg/ml and HbA1c at 9.80%.

The transthoracic cardiac ultrasound (TTE) showed a bi-atrial dilation predominant on the left, a thrombus in the left atria, non-dilated left ventricle (LV) non-hypertrophied (Figure 3). It also showed basal and median hypokinesia of the inferior, anterior and antero-septal walls, LV dysfunction with left ventricular ejection fraction assessed at 35% and high left filling pressures. The study of 2-dimension strain showed an alteration of the predominant longitudinal strain at the basal and median segments while respecting the apical segments, with an overall longitudinal strain altered at -9.8% (Figure 4). The right ventricle had a reduced cavity, its systolic function was moderately impaired. The measurement of pulmonary arterial pressure showed moderate pulmonary arterial hypertension with systolic pulmonary artery pressure at 47 mmHg. There was a low abundant pericardial effusion (Figure 5).

The biopsy of the accessory salivary glands ruled out any lesion in favor of amyloid involvement.

The MRI objectified an aspect of RCM with the presence of small foci of myocardial fibrosis in the anterior and inferior walls, a bi-atrial dilation, a left intra-atrial thrombus, a moderate LV dysfunction and eliminated the differential diagnosis of Constrictive pericarditis (Figure 6).

We completed the family investigation and found that her daughter has a non-obstructive hypertrophy cardiomyopathy with preserved systolic function and a restrictive LV filling profile. A Targeted Sanger DNA sequencing revealed the same pathogenic missense mutation in MYH7 gene (c. 1477A>G in heterozygous state (exon 15)) in our patient, her daughter, and the family members.
The patient received treatment for her congestive heart failure with loop diuretics, spironolactone and antagonist conversion enzyme inhibitors. A rhythm-controlled strategy was pursued for her atrial flutter. The patient was put on low-molecular-weight-heparin relayed later by rivaroxaban, cordarone, digoxin and beta blockers.

Figure 1: Electrocardiogram showing low voltage, a typical atrial flutter at variable conduction and a complete left bundle branch block.

Figure 2: Chest radiography showing pulmonary edema and cardiomegaly.

Figure 3: TTE apical 4-chamber view showing massively enlarged left and right atria.
Figure 4: TTE apical 2-chamber view showing a left atria thrombus.

Figure 5: TTE two-dimensional strain showing an alteration of the predominant longitudinal strain at the basal and median segments while respecting the apical segments, with an overall longitudinal strain altered at -9.8%.

Figure 6: Cardiac MRI 2-chamber view showing a bi-atrial dilatation and small foci of myocardial fibrosis in the basal and medial segment of the inferior wall.
Figure 7: Cardiac MRI 4-chamber view showing a bi-atrial dilatation, a left atrial thrombus, a non-dilated LV, a low abundant pericardial effusion, and thin and uncalcified pericardial leaflets.

Video 1 (TTE 1): TTE apical 4-chamber view showing massively enlarged left and right atria.

Video 2 (TTE 2): TTE apical 2-chamber view showing a left atria thrombus.
A few weeks later, she presented with a syncope on complete atrioventricular block. A triple chamber pace maker was installed. She had a radiofrequency ablation of atrial flutter after dissolution of the left atrial thrombus. After treatment, she returned to a sinus rhythm, with no recurrence of her arrhythmia.

**Discussion:**

RCM is classified into 2 types: idiopathic RCMs and secondary RCMs such as amyloidosis (in 50% of cases), hypereosinophilia syndrome and endomyocardial fibrosis (Langlard, 2004). In 36% of cases, the pathology remains idiopathic and is part of a familial form of genetic origin in 10% of cases.

Familial RCM is caused by mutation of cytoskeletal and sarcomere genes with autosomal dominant inheritance, and variable penetrance due to epigenetics and environmental factors (Nafissi et al, 2019). They are characterized by high allelic, genetic and phenotypic variability which can be observed between different families and between individuals belonging to the same family (Willoff et al, 2019). 80% of RCM cases have de novo mutations, compared to other CMs (Parrott et al, 2020). TNNT1’s mutation is the most frequent cause of RCMs (8-10% of cases) (Mogensen et al, 2003). MYH7 mutation has rarely been found in RCM (6.7%) (Kapoor et al, 2017), but in this family, another mutation of this gene (c.1477A> G (p. Met493Val)) reported to be causative in HCM (OMIM 160760) has been found (Richard et al, 2003).

In her daughter, we found in TTE a non-obstructive MHC with a restrictive LV filling profile, making it a familial form of CM with variable phenotypic expression.

Genetic screening should be considered to help identify patients at risk in families with suspected familial transmission, thus avoiding diagnostic and therapeutic delay, and allowing better management of patients by anticipating complications and providing family genetic counseling.

Treatment is based on diuretics. It should avoid negative inotropic agents, and strive to maintain sinus rhythm. Definitive cardiac stimulation should be offered in cases of atrioventricular conduction disorder and bradyarrhythmia. Finally, heart transplantation can be offered in cases of refractory heart failure (Yancy et al, 2013).

The prognosis for familial RCM is generally good, their 5-year survival rate is 60%. The course can be fatal without treatment with a 5-year mortality rate of 30%.

MYH7 mutations seem to be associated with severe phenotypes, earlier age of onset and more pejorative evolution than other mutations.

The patient began to recover almost immediately after her hospitalization with significant improvement in symptoms and functional capacity. Her pacemaker is checked every 6 months, and she is regularly seen by her cardiologist for an echocardiographic follow up. We have recommended genetic screening for her first-degree relatives.

**Conclusions:**

The authors present a case of familial RCM by a MYH7 mutation in a patient with a global heart failure. The evaluation of familial RCM requires an understanding of its variable phenotypic expression and incomplete penetrance. Genetic testing for hereditary RCM should be considered when secondary causes have been excluded. A regular echocardiographic follow up is mandatory to detect early signs of heart failure.

We review the evaluation and management of restrictive cardiomyopathy with a focus on genetic etiologies.

**Learning Objectives**

1. Develop a differential diagnosis for RCM
2. Learn the Evaluation and management of RCM
3. Understand the genotypic and phenotypic similarities between hereditary RCM and HCM
4. Understand a variable phenotypic expression and an incomplete penetrance in a familial mutation
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