An unusual case of 11αB-crystallin (CRYAB) mutation as a cause of dilated cardiomyopathy with restrictive physiology: A Case Report and Focused Review of the Literature

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Introduction

The CRYAB gene encodes the protein Alpha-B-crystallin, or αB-crystallin, a protein belonging to the small heat shock family of proteins that has been linked to normal cardiac homeostasis as well as cardiomyopathies, among other diseases [1]. CRYAB, the causal gene, is 3.2 kilobases long and situated on chromosome 11 [2]. Although its role as a molecular chaperone for desmin is well established, it also engages in interactions with a diverse range of other proteins [1].

Mutations in the CRYAB gene have been associated with congenital cataracts, myopathies, neurodegenerative diseases, and besides with hypertrophic cardiomyopathy (HCM), and less commonly with dilated cardiomyopathy (DCM) and restrictive cardiomyopathy (RCM)[1,3-5].

However, the CRYAB association with DCM has recently emerged in the last decade, which is why it may not be included in the list of genetic mutations associated with DCM according to the most recent guidelines of the European Society of Cardiology (ESC) and some reviews in recent literature. However, increasing emerging observational evidence suggests an association with DCM. Below we describe the case of a patient who developed DCM whit restrictive physiology secondary to a heterozygous mutation of the CRYAB gene.

Case history/Examination

A 42-year-old man with a history of heart failure with a mildly reduced ejection fraction of 42% in whom the aetiology of it was under evaluation consulted the heart failure program at a university hospital. He was receiving standard heart failure medications with sacubitril/valsartan, carvedilol, spironolactone, and empaglifozin at maximum tolerable doses. Among his previous studies, a transthoracic echocardiogram showed a left ventricle with normal size and diameter, systolic dysfunction with a 43% left ventricular ejection fraction (LVEF), grade III diastolic dysfunction, severe tricuspid regurgitation, and moderate mitral regurgitation, along with severe biatrial enlargement and a high probability of pulmonary hypertension.

Besides, a cardiac magnetic resonance (CMR) with late gadolinium enhancement showed a left ventricle with mild dilatation and a decreased systolic function, without contractility disorders; however, with late generalised gadolinium endocardial enhancement with severe mitral regurgitation and moderate tricuspid regurgitation, also with a biatrial and right ventricle dilatation (Figure 1), suggesting a DCM with restrictive physiology taking also into account the previously transthoracic echocardiogram that was performed.

Because of this, secondary causes of DCM such as Chagas disease, alcoholic cardiomyopathy, drugs and toxins causing DCM, and also myocarditis and autoimmune disorders were ruled out. Besides, secondary causes of DCM such as Chagas disease, alcoholic cardiomyopathy, drugs and toxins causing DCM, myocarditis, and

autoimmune disorders were too ruled out. Coronary artery disease (CAD) was ruled out too after performing a coronary arteriography (Figure 2).

After holding a multidisciplinary medical meeting, the medical staff considered that the patient had a heart failure with mildly reduced ejection fraction due to a DCM with restrictive physiology from idiopathic or genetic aetiology, for which reason it was carried out a genetic testing of 76 cardiomyopathy genes, which ruled out which ruled out the very common, common, and less common mutation genes for DCM among other cardiomyopathies, according to the ESC guidelines[6]. Nevertheless, a heterozygous CRYAB mutation was detected as a potential cause of cardiomyopathy.

Consequently, after genetic counselling and also after performing research regarding this mutation, which was found, a DCM with restrictive physiology due to the CRYAB mutation were diagnosed, highlighting the fact that the CRYA mutation is a not common gene mutation related to DCM according to the most recent ESC guidelines[6].

Differential diagnosis, investigations and treatment

In relation to the differential diagnosis of neither ischaemic nor genetic secondary causes of DMC, certain pathologies that could cause it have been described [4,6]. These include:

- Infectious causes (post-myocarditis): Chagas disease, viral (enteroviruses, adenoviruses, echoviruses, herpes viruses, parvovirus B19, HIV, SARS-CoV-2), bacterial (Lyme disease), mycobacterial, and fungal.
- Toxic and overload causes: Ethanol, cocaine, amphetamines, ecstasy, cobalt, anabolic/androgenic steroids, haemochromatosis and other causes of iron overload.
- Endocrinology causes: Hypo and hyperthyroidism, Cushing/Adisson disease, phaeochromocytoma, acromegaly, diabetes mellitus.
- Nutritional deficiency causes: Selenium, thiamine, zinc, copper, and carnitine deficiencies have been described.
- Drugs: Antineoplasic drugs and mainly anthracyclines, but also antimetabolites, alkylating agents, taxol, hypomethylating agents, monoclonal antibodies, tyrosine kinase inhibitors, and immunomodulating agents. Besides, psychiatric drugs like clozapine, olanzapine, chlorpromazine, risperidone, lithium, methylphenidate, and tricyclic antidepressants. Finally, other drugs like all-trans retinoic acid, antiretroviral agents, and phenothiazines have been described.
- Peripartum

After reviewing the diagnostic criteria and performing an exhaustive interrogation and physical examination, and after performing the laboratory tests indicated for these diagnoses, these conditions were ruled out. Therefore, it is important to keep in mind that within the diagnostic approach of this cardiomyopathy, secondary non-genetic diseases must be ruled out; likewise, carrying out an adequate family pedigree of the patient's relatives in order to guide a possible genetic origin of the cardiomyopathy.

In our case, no first- or second-degree relatives of the patient had a history of cardiomyopathies or other relevant diseases, which is why it was considered de novo mutation.

Outcome and follow up

During follow-up, despite the treatment of heart failure with optimal medical therapy with foundational therapy and cardiac rehabilitation among others, his mitral and tricuspid regurgitations progressed to a worse severe grade, preventing an improvement in the symptoms reported by the patient, with a gradual increase in symptoms, which is why after holding a new medical meeting, it was considered that he was a candidate for mitral valve replacement and tricuspid valve plasty. Besides, a myocardial biopsy was performed during the surgery.

Although, in an interesting way, the myocardial biopsy revealed endocardial and subendocardial fibrosis with anisonucleosis of the cardiomyocytes, also with altered architecture from the myocardial fibres (Figure

3). Currently the patient is receiving optimal medical therapy for his heart failure and is undergoing cardiac rehabilitation.

Discussion

Regarding cardiomyopathies, the CRYAB mutation gene has been linked to HCM as a common mutation gene, according to the ESC guidelines[6]. However, after performing a review of the available medical literature in the major clinical databases (Pubmed, Google Scholar, and Scielo), we found some manuscripts describing a relation between the CYRAB mutation and DCM in humans [2,4,7,8].

Regarding DCM It's important to keep in mind that it's defined by the presence of left ventricular dilatation and systolic dysfunction unexplained solely by abnormal loading conditions or coronary artery disease (CAD) [6]. In our case abnormal loading conditions were ruled out, as CAD by right and left coronary arteriography without epicardial lesions.

According to epidemiology, familial DCM accounts for 30–40% of all DCM cases; in 20–40% of those cases, a gene has been found[4,6]. According to the ESC guidelines the very common, common or less common genes associated with DMC include ABCC9, ACTC1, ACTN2, ANKRD1, BAG3, CSRP3, CTF1, DES, DMD, DSG2, DSP, DTNA, EYA4, FLNC, GATAD1, ILK, JPH2, LAMA4, LDB3, LMNA, LRRC10, MIB1, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYPN, NEBL, NEXN, NKX2-5,NPPA, OBSCN, PDLIM3, PKP2, PLEKHM2,PLN, PRDM16, PSEN1, PSEN2, RBM20, SCN5A, SGCD, TBX20, TCAP, TMEM43, TMP0, TMNC1, TNNI3, TNNI3K, TNNT2, TPM1, TTN and VCL[6].

Despite the CRYAB mutation not being included in the previous list, in the last years this mutation has been described as a pathogenic mutation in DCM in several articles [2,4,7,8] . In our case, a heterozygous CRYAB mutation was detected after excluding other causes of secondary DCM and may be as novo due to the absence of documented cardiomyopathies in his relatives.

Respect the physiopathology why this mutation causes cardiomyopathy; in mouse models it has been found that an R120G missense mutation causes "desmin-related cardiomyopathy," which is characterised by the formation of aggregates of oligomeric amyloid containing CRYAB and desmin with accumulation of them within cardiac muscle, generating mitochondrial deficiencies, activation of apoptosis, and heart failure[9,10]. These oligomeric amyloid intermediates have also been seen in cardiomyocytes from many humans with dilated and hypertrophic cardiomyopathies [9,10].

Besides, it has even been shown that this mutation in vitro cardiomyocytes leads to mitochondrial dysfunction and subsequent apoptosis, which eventually results in cardiomyocyte death, dilatation, and heart failure [11].

Regarding the treatment of chronic heart failure with reduced ejection fraction, it must be according to the international guidelines provided by the ESC and ACC guidelines, among other relevant guidelines[12-14]. However, regarding the treatment of genetic DCM, it's important to assess if the patient carries some specific mutations associated with increased risk of sudden cardiac death, like FLNC, DES, DSP, PLN, LMNA, TMEM43, and RMB20, among others[6]. In our case these mutations were ruled out.

Although predicting SCD is a challenging aspect of the clinical care of patients with DCM mainly in primary prevention because in secondary prevention they have demonstrated to reduce mortality among survivors of cardiac arrest and in whom have experienced sustained ventricular arrhythmias with haemodynamic compromise [6].

Nevertheless, a LEVF [?]35% has been reported as an independent risk marker of all cause and cardiac death in DCM despite its modest ability to identify DCM patients with a higher risk of SCD; also, DCM patients harbouring DCM-causing variants in high-risk genes (LMNA, EMD, TMEM43, DSP, RBM20, PLN, FLNC-truncating variants) should be considered as patients with a high-risk genetic background for SCD, and primary prevention ICD implantation should be considered with LVEF thresholds higher than 35% [6]. In our case, these conditions were absent, so actually an indication to implant an ICD for primary prevention is not considered.

Finally, in an interesting way, voluntary exercises have shown a significant improvement in survival among a mouse model, also reducing the accumulation of preamyloid due to the CRYAB mutation, slowing the progression of heart failure in this animal model. Nevertheless, more research is needed to confirm this finding in humans[15].

Conclusions

Even though CRYAB mutations have been linked mainly with HCM according to the ESC guidelines, new emerging evidence relates it in DCM cases, whereby, in the presence of a DCM, this mutation may be considered as an unusual potential cause to be screened within the diagnostic approach in the genetic test screening.

Author contribution statement

Porras Bueno Cristian Orlando: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing (original draft), writing review, and editing.

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Rios Dueñas Edgar Giovanni: conceptualization, data curation, formal analysis, investigation, writing (original draft), review, and editing.

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