Int. j. adv. multidisc. res. stud. 2024; 4(3):612-615

Received: 04-04-2024
Accepted: 14-05-2024

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

A Case of Dilated Cardiomyopathy caused by TTN Truncating Mutation

[1] Hao Thai Phan
[1] Pham Ngoc Thach University of Medicine, HCM City, Vietnam
[1] HCMC Hospital for Rehabilitation-Professional Diseases, Vietnam

DOI: https://doi.org/10.62225/2583049X.2024.4.3.2830
Corresponding Author: **Hao Thai Phan**

Abstract
Dilated cardiomyopathy is one of the leading causes of heart failure with high morbidity and mortality. Although more than 40 genes have been reported to cause dilated cardiomyopathy, the role of genetic testing in clinical practice is not well defined. Mutations in the titin (TTN) gene represent an important subset of known disease-causing mutations associated with dilated cardiomyopathy. TTN truncating mutations are a common cause of dilated cardiomyopathy, occurring in approximately 25% of familial cases of idiopathic dilated cardiomyopathy and in 18% of sporadic cases. Here, we presented a case of dilated cardiomyopathy caused by TTN mutation in 20-year-old male.

Keywords: Dilated Cardiomyopathy, Genetics, TTN Truncating Mutation

Introduction

Dilated cardiomyopathy (DCM) has an estimated population prevalence of 1:250 and is the commonest cause for heart transplantation worldwide [1, 2]. More than 25% of patients with DCM have a genetic predisposition [2, 3]. and emerging data suggest that genotype has an important impact on prognosis and therapy [4].

Truncating variants in the TTN gene (TTNtv), encoding the giant protein titin, are the commonest genetic subtype of DCM, accounting for up to 25% of cases [5]. Titin is an integral sarcomeric protein involved in passive force transmission and plays essential roles in sarcomere organization, elasticity, and cell signaling [6]. In some studies, TTNtv associated with DCM appear to be highly enriched in the A band [5]. but more recently, TTNtv mutations in other constitutively expressed exonic regions have also been implicated in DCM [7, 8]. In addition, previous studies on TTNtv are inconsistent with respect to arrhythmia burden [7], response to optimal medical therapy (OMT), impact of mutation location [7], and prognosis [7]. In this study, we report a case of dilated cardiomyopathy caused by TTN mutation in 20-year-old male.

Case Presentation

This case involved a 20-year-old man who presented dyspnea for two days duration. His history diseases was noraml. Physical examination was remarkable for displaced apical impulse and jugular vein distention. Electrocardiography showed sinus rhythm 70 bpm, low QRS voltage in limb leads, left ventricular enlargement. Chest Xrays showed a large cardiac shadow (Fig 1). Transthoracic echocardiography revealed dilated 4 chambers, reduced left ventricular ejection fraction 43% (Simpson Biplane EF 14%), global left ventricular hypokinesia, moderate mitral regurgitation, moderate triscupid regurgitation, systolic pulmonary artery pressure PAPs=21 mmHg (Fig 2). Cardiac CT revealed dilated left ventricular, dilated left atrium. Normal coronary arteries (Fig 3). Laboratory tests including mild elevated TSH 6.6 µIU/mL (0.27-4.20 µIU/mL), normal free T4 1.6 ng/mL (0.71-1.85 ng/mL), normal creatinine 1.2 mg/dL, AST 30.35 U/L, ALT 54.3 U/L, high NT-proBNP= 5447 pg/ml. Genetic testing showed a TTN gene mutation on chromosome 2, heterozygous, truncating type: NM_001267550.2: c.58870C>T (NP_001254479.2: p.Arg19624Ter).

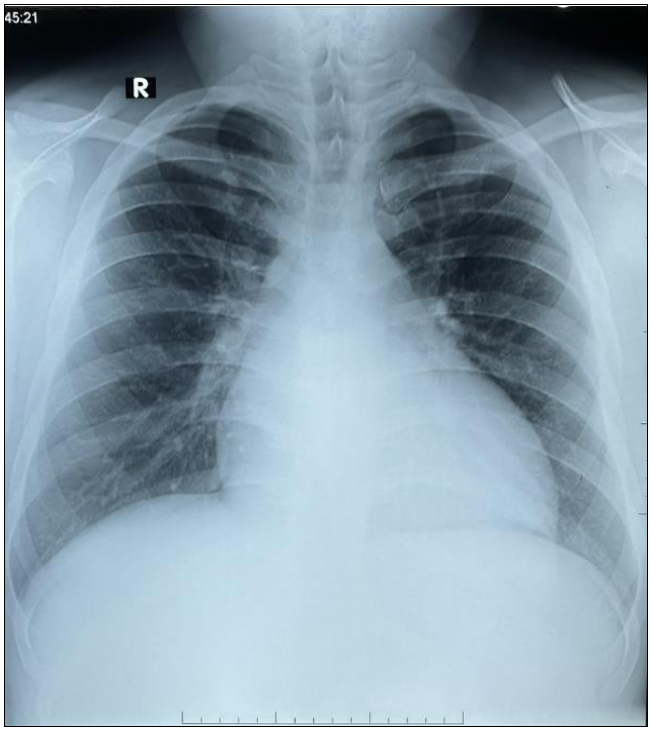

Fig 1: Chest Xrays showed a large cardiac shadow

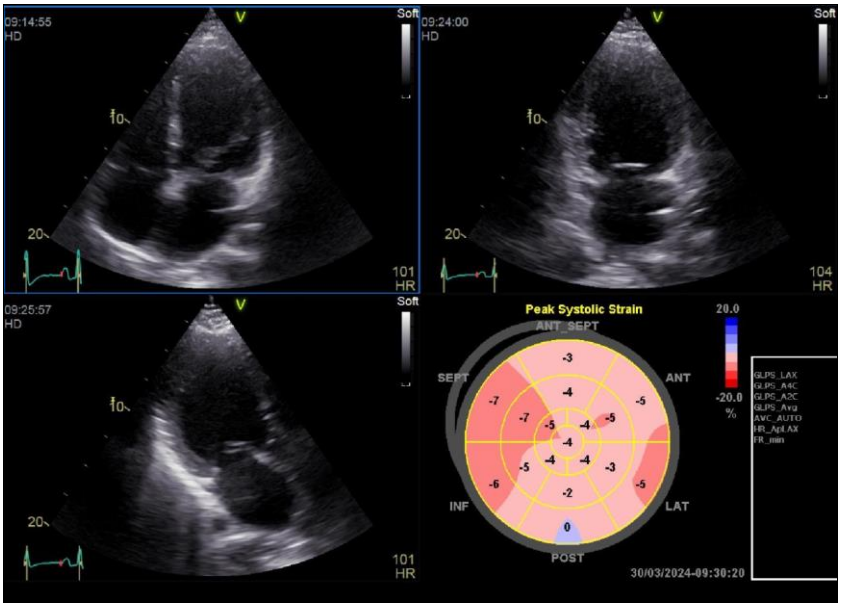

Fig 2: Echocardiography showed dilated 4 chambers, global left ventricular hypokinesia

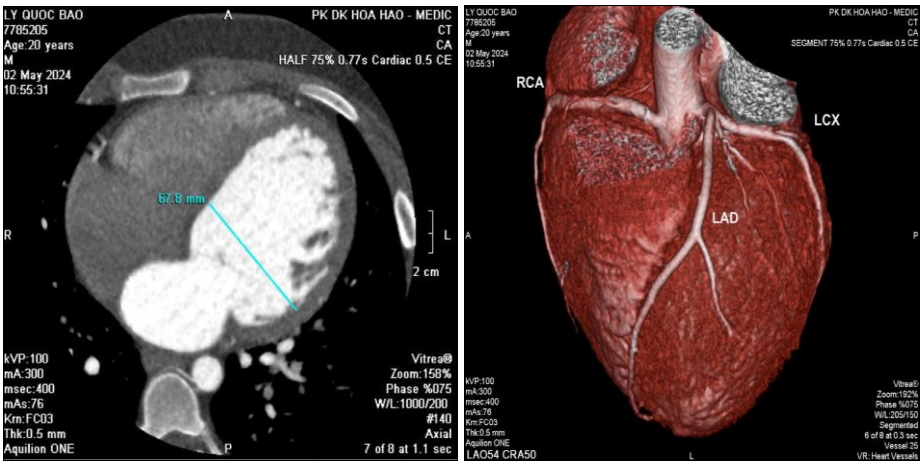

Fig 3: Cardiac CT revealed dilated left ventricular, dilated left atrium. Normal coronary arteries

He received standard treatment for heart failure with 4 drugs (Empagliflozin, Spironolactone, Carvedilol, Sacubitril/Valsartan). He gradually improved after 1 month of follow-up.

Discussion

Titin is an essential component of the sarcomere, providing most of the passive force [9], and plays crucial roles in cardiac and skeletal muscle development, structure, elasticity, and cell signaling [10]. Doubts were raised about the pathogenicity of truncating TTN variants as these were also detected in supposedly healthy control cases [11]. However, in a study using a large data set [12], it was found that tTTN variants associated with DCM are found mainly in highly expressed exons of the cardiac titin isoforms N2B and N2BA, which are situated predominantly in the A-band, whilst the tTTN variants found in control cases are mainly found in other TTN regions. These selected tTTN variants have a high a priori (93%) chance of being pathogenic [13]. This was corroborated by another study which found fewer A-band tTTN variants in the general population than previously reported [14] and an a priori chance of pathogenicity of nearly 98% [15]. Because tTTN variants may still also be found in control populations, one may surmise that some tTTN mutations do not induce pathology by itself, i.e. are of low penetrance, but need a second hit as we recently demonstrated in peripartum-related cardiomyopathy and TTN mutations [15]. This example of interaction of a mutation with low penetrance and an environmental factor (pregnancy) suggests that some tTTN mutations may only induce pathology at a later stage in life or cause very mild changes so that apparent controls may have subtle signs of cardiomyopathy which have gone undetected. These findings contrast sharply with one of the other main genetic causes of DCM, mutations in the gene encoding lamin A/C (LMNA) [16]. Known cardiac disease-causing mutations in LMNA almost invariably induce phenotypic expression of the disease such as atrioventricular (AV) block, atrial fibrillation (AF), and eventually severe DCM [17] at relatively younger ages. In this case we report a TTN gene mutation on chromosome 2, heterozygous, truncating type: NM_001267550.2: c.58870C>T (NP_001254479.2: p.Arg19624Ter), this was the first mutation in TTN gene. This suggests that knowledge of the underlying gene defect in DCM identifies clinically meaningful subtypes of DCM that have different course and prognosis, and possibly a different response to therapy.

Conclusion

In conclusion, dilated cardiomyopathy mutations may be present in early onset dilated cardiomyopathy cases, and research studies designed to identify and characterize genetic cause in dilated cardiomyopathy is warranted. Clinical genetic testing may be considered in patients with early onset dilated cardiomyopathy for diagnosis confirmation. Incorporation of sequencing approaches that detect TTN truncations into genetic testing for dilated cardiomyopathy should substantially increase test sensitivity, thereby allowing earlier diagnosis and therapeutic intervention for many patients with dilated cardiomyopathy. Defining the functional effects of TTN truncating mutations should improve our understanding of the pathophysiology of dilated cardiomyopathy.

Author contributions

The author wrote the manuscript. The author have read, reviewed, and approved the article.

Funding No funding was received for this article.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki. The patient gave informed consent, and the patient's anonymity was preserved.

Consent for publication

Written informed consent for publication was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The author declare that they have no competing interests.

References

1. Towbin J, Bowles NJN. The failing heart. 2002; 415(6868):227-233.
2. Hershberger RE, Hedges DJ, Morales AJNrc. Dilated cardiomyopathy: The complexity of a diverse genetic architecture. 2013; 10(9):531-547.
3. De Gonzalo-Calvo D, Quezada M, Campuzano O, *et al*. Familial dilated cardiomyopathy: A multidisciplinary entity, from basic screening to novel circulating biomarkers. 2017; 228:870-880.
4. Wahbi K, Ben Yaou R, Gandjbakhch E, *et al*. Development and validation of a new risk prediction score for life-threatening ventricular tachyarrhythmias in laminopathies. 2019; 140(4):293-302.
5. Herman DS, Lam L, Taylor MR, *et al*. Truncations of titin causing dilated cardiomyopathy. 2012; 366(7):619-628.
6. Granzier HL, Irving TCJBj. Passive tension in cardiac muscle: contribution of collagen, titin, microtubules, and intermediate filaments. 1995; 68(3):1027-1044.
7. Roberts AM, Ware JS, Herman DS, *et al*. Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease. 2015; 7(270):270ra6-270ra6.
8. Schafer S, De Marvao A, Adami E, *et al*. Titin-truncating variants affect heart function in disease cohorts and the general population. 2017; 49(1):46-53.
9. Granzier HL, Irving TC. Passive tension in cardiac muscle: Contribution of collagen, titin, microtubules, and intermediate filaments. Biophysical Journal. 1995; 68(3):1027-1044. Doi:10.1016/s0006-3495(95)80278-x
10. Chauveau C, Bonnemann CG, Julien C, *et al*. Recessive TTN truncating mutations define novel forms of core myopathy with heart disease. Human Molecular Genetics. 2013; 23(4):980-991. Doi: 10.1093/hmg/ddt494 %J Human Molecular Genetics
11. Golbus JR, Puckelwartz MJ, Fahrenbach JP, Dellefave-Castillo LM, Wolfgeher D, McNally EM. Population-based variation in cardiomyopathy genes. Circulation Cardiovascular genetics. 2012; 5(4):391-399. Doi:

10.1161/circgenetics.112.962928
12. Roberts AM, Ware JS, Herman DS, *et al*. Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease. Science Translational Medicine. 2015; 7(270):270ra6. Doi: 10.1126/scitranslmed.3010134
13. Watkins H. Tackling the achilles' heel of genetic testing. Science Translational medicine. 2015; 7(270):270fs1. Doi: 10.1126/scitranslmed.aaa4276
14. Akinrinade O, Koskenvuo JW, Alastalo TP. Prevalence of Titin Truncating Variants in General Population. PloS one. 2015; 10(12):e0145284. Doi: 10.1371/journal.pone.0145284
15. Ware JS, Li J, Mazaika E, *et al*. Shared Genetic Predisposition in Peripartum and Dilated Cardiomyopathies. The New England Journal of Medicine. 2016; 374(3):233-41. Doi: 10.1056/NEJMoa1505517
16. Fatkin D, MacRae C, Sasaki T, *et al*. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. The New England Journal of Medicine. 1999; 341(23):1715-1724. Doi: 10.1056/nejm199912023412302
17. Van Rijsingen IA, Nannenberg EA, Arbustini E, *et al*. Gender-specific differences in major cardiac events and mortality in lamin A/C mutation carriers. European Journal of Heart Failure. 2013; 15(4):376-384. Doi: 10.1093/eurjhf/hfs191