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CASE REPORT

A case of dilated cardiomyopathy caused by TNNT2 mutation diagnosed delayed

Hao Thai Phan, MD, PhD

Pham Ngoc Thach University of Medicine, HCM city, Vietnam
HCMC Hospital for Rehabilitation-Professional Diseases, Vietnam.

phanthaihao@yahoo.com; haopt@pnt.edu.vn

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 troponin T (TNNT2) gene represent an important subset of known disease-causing mutations associated with dilated cardiomyopathy. Mutations in TNNT2, encoding cardiac troponin T, commonly shows early onset, aggressive dilated cardiomyopathy. This observation may influence the decision of whether to undertake clinical genetic testing for TNNT2 in later onset dilated cardiomyopathy. Further, the trigger for late onset dilated cardiomyopathy remains enigmatic. Here, we presented a case of dilated cardiomyopathy caused by TNNT2 mutation in 59-year-old male.

Keywords: dilated cardiomyopathy, genetics, TNNT2 mutation.

Introduction

Idiopathic or primary dilated cardiomyopathy (DCM) is one of the leading causes of heart failure with high morbidity and mortality[1,2]. The prevalence of DCM is 36.5 cases per 100,000 individuals, and 30–50% of all cases are diagnosed as a familial form of DCM[2, 3, 4]. Recent studies have reported that more than 40 genes, including 2 X-linked genes, are associated with DCM[5,6]. In the vast majority of cases, these genes encode for sarcomeric contractile proteins such as troponin T (TNNT2), troponin I (TNNI3), and cardiac α-actin (ACTC)[7, 8].

The TNNT2 gene encodes the thin-filament contractile protein cardiac troponin T, which links the troponin complex to tropomyosin in the sarcomere[9]. TNNT2 contains 16 exons, is located on chromosome 1q32, and comprises 25 kb of the genome. Recent data have indicated that TNNT2 mutations are associated with DCM and that the overall frequency of TNNT2 mutations in familial DCM is approximately 3–6%[10,11]. Up to 50% of IDC is familial (familial dilated cardiomyopathy, FDC) and a disease-causing mutation in any of more than 30 genes can be identified in 25%–30% of cases[12, 13, 14]. Emerging evidence also suggests that mutations can be present regardless of family history[14,15,16,17] and in some cases multiple mutations may be at play[14,15,17]. All patterns of inheritance have been reported, however, autosomal dominant with reduced penetrance and variable expressivity is most commonly observed[12,13]. Genocopies caused by syndromic disease such as HFE-related hemochromatosis are also possible, but rarer causes.

Case Presentation

This case involved a 59-year-old man who presented dyspnea for two days duration. His history diseases were hypertension. Physical examination was remarkable for displaced apical impulse and jugular vein distention and pedal edema. Electrocardiography showed atrial fibrillation 74 bpm, low QRS voltage in limb leads (**Figure 1**). Chest Xrays showed a large cardiac shadow, signs of pulmonary venous congestion (**Figure 2**). Transthoracic echocardiography revealed dilated left ventricular, reduced left ventricular ejection fraction 33%, global left ventricular hypokinesia, moderate mitral regurgitation, moderate triscupid regurgitation, increased systolic pulmonary artery pressure PAPs=40 mmHg. Cardiac CT revealed dilated left ventricular, dilated left atrium. Normal coronary arteries (**Figure 3**). Laboratory tests including normal TSH 0,703µIU/mL, normal free T4 1.59ng/mL, normal creatinine 80.9 µmol/L, AST 40.1 U/L, ALT 37.3 U/L, high NT-proBNP= 2573 pg/ml. Genetic testing showed a dominant TNNT2 gene mutation on chromosome 1, heterozygous, inframe deletion type: NM_000364.4: c.517_519del (NP_000355.2: p.Glu173del).

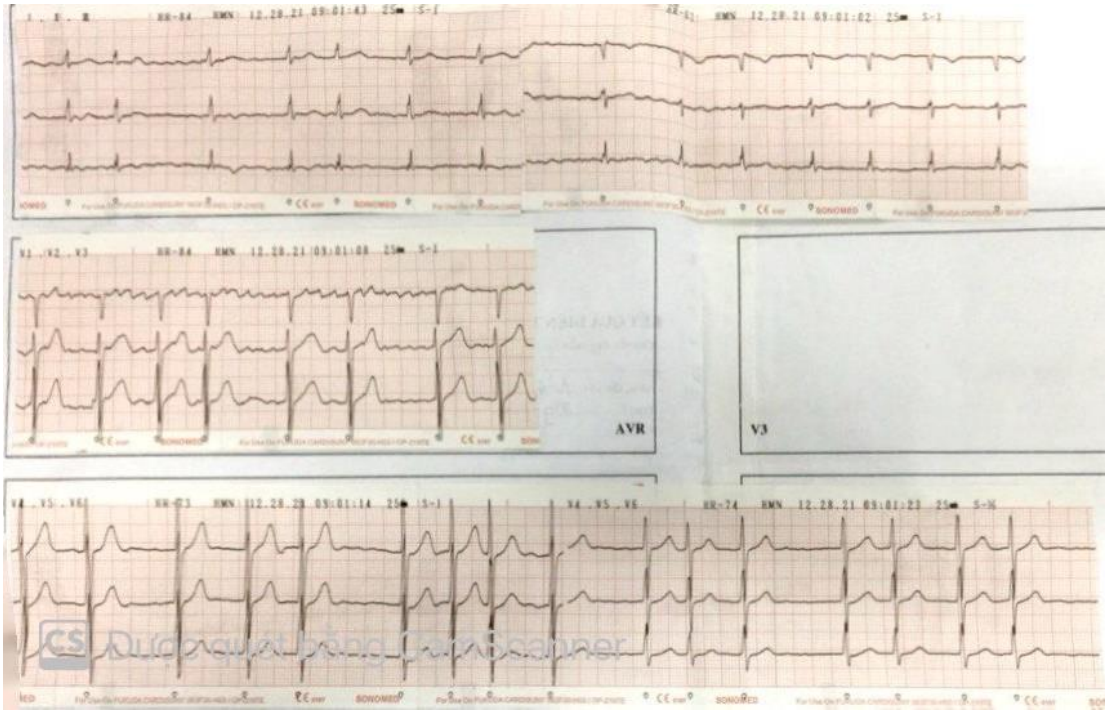

Figure 1. Electrocardiography showed atrial fibrillation 74 bpm, low QRS voltage in limb leads.

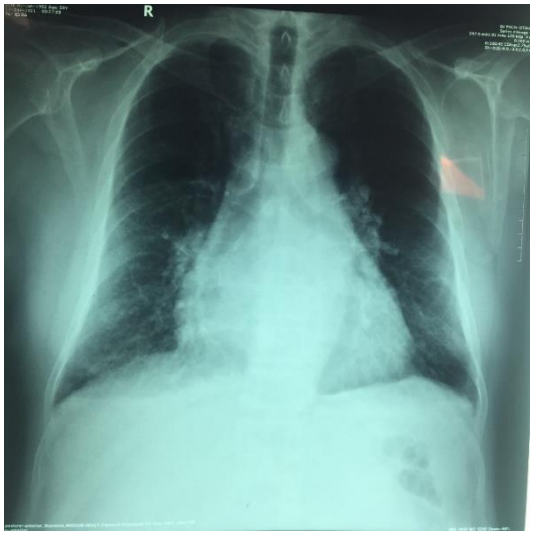

Figure 2. Chest Xrays showed a large cardiac shadow, signs of pulmonary venous congestion.

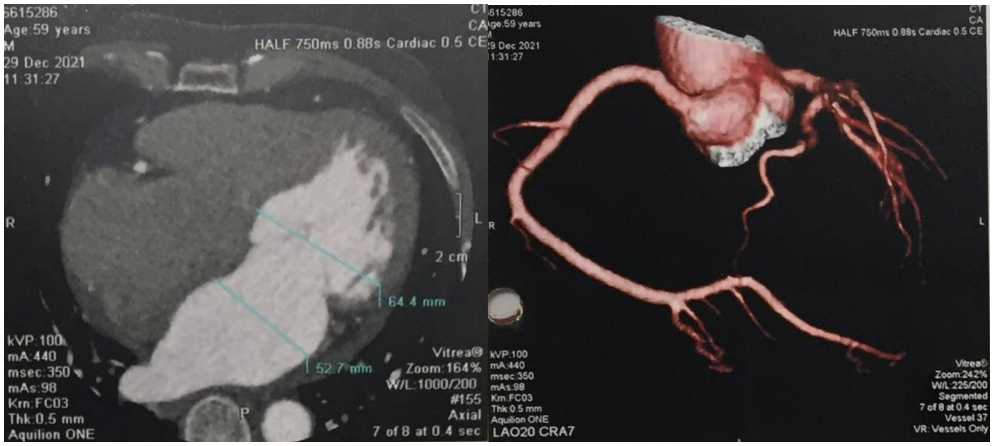

Figure 3. Cardiac CT revealed dilated left ventricular, dilated left atrium. Normal coronary arteries.

He received standard treatment for heart failure with 4 drugs (Empagliflozin, Spironolactone, Carvedilol, Sacubitril/ Valsartan), Ivabradine and the diuretic furosemide. He gradually improved and was completely healthy after 2 years of follow-up.

Discussion

This is novel report of late onset, dilated cardiomyopathy at age 59 caused by a TNNT2 mutation, accompanied by life-threatening progressive heart failure requiring cardiac transplantation, raises clinical and mechanistic questions regarding the timing of onset of adult onset partially penetrant Mendelian rare variant disease. The age of onset of 59 years presented here contrasts distinctly with the median age of onset of 26 years in the 55 previously reported TNNT2 mutation carriers, or the median age of 21 at which heart transplantation, LVAD or death occurred[15,17,20] and others [18,19,21] have previously pointed out that the usual age of onset of dilated cardiomyopathy -causing TNNT2 mutations is within the first 3 decades of life. The clinical evidence that this patient had dilated cardiomyopathy and heart failure is incontrovertible: her cardiac function was reduced (ejection fraction 33%). Because of the recent guideline suggestions that molecular genetic testing should be considered even in apparently dilated cardiomyopathy, usually termed idiopathic dilated cardiomyopathy[12] the proband underwent molecular genetic testing for 19 genes associated with dilated cardiomyopathy in a commercial laboratory; a rare TNNT2 nonsynonymous variant was identifi ed. The molecular genetic evidence is also clear: a nonsynonymous mutation not found in >1,000 control DNAs and identifi ed in a gene known to harbor dilated cardiomyopathy -causing variants[15,17, 21] indicates that it is possibly disease-causing, as we have attributed to such cases in our prior studies[14,15]. When combined with the functional evidence presented above, the collective evidence is compelling that the identified TNNT2 mutation was highly likely relevant causative factor for his dilated cardiomyopathy.

Conclusion

In conclusion, dilated cardiomyopathy mutations may be present in late 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 late onset dilated cardiomyopathy for diagnosis confirmation. Ultimately, high throughput exome or whole genome sequencing in large cohorts will be required to evaluate the extent to which genetic susceptibility contributes to late onset dilated cardiomyopathy.

Competing interests Statement:

The author declare that they have no competing interests.

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Author contributions:

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

ORCID:

0000-0001-5306-4065.

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