

Case Report

Titin Variant Cardiomyopathy Unveiled by Rigorous Aerobic Exercise

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Abstract

A symptomatic 48-year-old woman, distance runner, was diagnosed with a dilated cardiomyopathy and found to have a likely pathogenic Titin truncating variant gene. Symptoms and left ventricular volumes improved months after withdrawal from running. Heavy aerobic exercise may unveil Titin truncating variant induced cardiomyopathy.

Keywords: Titin; Dilated cardiomyopathy; Arrhythmia; Genetic testing; Sudden cardiac death

Abbreviations

TTNtv: Truncating Variants of Titin; DCM: Dilated Cardiomyopathy; VPC: Ventricular Premature Contractions; EKG: Electrocardiogram; LVDD: Left Ventricular end Diastolic Dimension; LVEF: Left Ventricular Ejection Fraction; CMRI: Cardiac Magnetic Resonance Imaging; LGE: Late Gadolinium Enhancement; ICD: Implantable Cardioverter-Defibrillator

Case Presentation

Truncating Variants of Titin (TTNtv) account for 25% of all familial idiopathic Dilated Cardiomyopathy (DCM) cases [1,2]. Further, apparently healthy TTNtv carriers are at increased risk of developing symptomatic DCM after exposure to cardio-toxic or hemodynamic stress like chemotherapy, excessive alcohol consumption, or pregnancy [3-5]. The present report examines the outpatient course of a distance runner who was seen for new symptoms of fatigue and dizziness and diagnosed with a TTNtv DCM. The patient's symptoms resolved and left ventricular function and dimensions improved a few months after the patient curtailed her heavy running schedule.

Initial visit

A 48-year-old woman without past medical history outside of two uneventful pregnancies consulted with cardiology for new onset of fatigue and dizziness that occurred once or twice per week, lasted several minutes, and was unrelated to exertion or position. The patient was a distance runner for 20 years and was no longer able to run her

customary 20 miles to 25 miles per week. Physical examination was unremarkable. Her body mass index was 23 Kg/m², heart rate was 65 beats/minute, and blood pressure was 107/73 mmHg. Her blood counts, sedimentation rate, renal function, connective tissue panel, high sensitivity C-reactive protein, and thyroid function tests were all within normal range. NT-pro-BNP was elevated at 1020 pg/mL (Upper normal 450 pg/mL). Human immune deficiency and hepatitis viral serologies were negative. Sinus rhythm with frequent multifocal Ventricular Premature Contractions (VPCs) was noted on Electrocardiogram (EKG). Left Ventricular end Diastolic Dimension (LVDD) was 64 mm, Left Ventricular Ejection Fraction (LVEF) 35% by 2D echocardiography with bi-atrial enlargement, moderate mitral and tricuspid regurgitation and grade two diastolic dysfunction. The clinical impression was familial DCM. Familial pedigree, genetic testing/counseling, exercise stress test, 24-hour Holter monitoring, and Cardiac Magnetic Resonance Imaging (CMRI) were obtained.

Follow up

Familial pedigree confirmed that the patient's father and paternal grandfather died suddenly and unexpectedly in their fifties. The exact circumstances of these two sudden deaths could not be ascertained as autopsies were not performed. Exercising on a treadmill with a ramp protocol, the patient reached a peak heart rate of 142 beats/minute with frequent multifocal VPCs. Her functional capacity was estimated at 14 metabolic equivalents. She had a normal blood pressure response to exercise and no ischemic changes on EKG. Left ventricular end-diastolic and end-systolic volumes were 246 mL and 152 mL and right and left ventricular ejection fractions were 50% and 38% by CMRI; there was no Late Gadolinium Enhancement (LGE). Holter monitoring showed 16,001 multifocal VPCs/24 hours. Clinical genetic testing for cardiomyopathy with second-generation sequencing showed a likely pathogenic variant, c.79041del (p.Val26348Leufs*5) in *Titin* (TTN) gene: a deletion that causes a change from valine to isoleucine resulting in frameshift in the protein five amino acids down from leucine that ultimately causes a premature truncation of the protein. Positron emission tomography revealed no 18-fluorodeoxyglucose myocardial activity. The patient's two sedentary daughters tested positive for the c. 79041del (p.Val26348Leufs*5) TTN variant and both had normal LVEF and LVDD by 2D echocardiography. Arrhythmogenic right

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ventricular cardiomyopathy was excluded as a diagnosis based on lack of criteria from EKG and CMRI (Figure 1).

Treatment

The patient was advised to curtail her running and heavy exertion. She did not tolerate beta-adrenergic receptor blockade with metoprolol succinate due to fatigue/bradycardia. She was initially continued on lisinopril 10 mg daily. Amiodarone therapy was initiated at an oral daily dose of 400 mg. Eight weeks after initiation of amiodarone therapy, a second Holter revealed 19 VPCs/24 hours. Over these same two months she did not experience any episodes of dizziness and as such amiodarone was discontinued. Three months after discontinuation of amiodarone, a third Holter was obtained that recorded 29 VPCs/24 hours. Seven months after the initial visit, her left ventricular end diastolic and end systolic volumes were 214 mL and 121 mL by repeat CMRI (Figure 2); right ventricular ejection fraction was unchanged and LVEF was 43%. At this time, five months after discontinuation of amiodarone, a fourth Holter was obtained and noted 44 VPCs/24 hours. The patient ultimately received a subcutaneous Implantable Cardioverter-Defibrillator (ICD).

Comments

Titin is the largest protein in the sarcomere. It contains four major domains (Z-disk, I-Band A-band and M-band) that extend from the Z line to the M line. It provides most of the passive force and modulates Ca^{++} sensitivity in active tension [6]. Due to the size and complexity of the *TTN* gene, next generation sequencing technologies are used to search for mutations [7]. Mutations in the A-band *TTN* are the predominant genetic cause of familial DCM [8]. Titin truncating variants account for 25% of all familial DCM cases and are present in 2% to 3% of the general population. To what extent a *TTN*tv

corresponds to a precise phenotype is unclear and likely depends on the presence of other mutations or external factors such as pregnancy, chemotherapy, excessive alcohol, and possibly sustained aerobic exercise [3-5]. The most commonly reported phenotype of *TTN*tv fits that of our patient: a mild form of DCM with LVEF ranging from 30% to 40% and a recognized increased risk of ventricular arrhythmia that is independent of traditional arrhythmic risks factors [9-13].

Most DCM patients with a LVEF greater than 35% have a relatively low risk of sudden cardiac death secondary to ventricular arrhythmia and do not routinely receive ICDs. This patient was recommended for ICD given that *TTN*tv cardiomyopathy patients seem to have an increased risk of ventricular arrhythmias [13], along with the observed high burden of VPCs and family history concerning for two members with possible sudden cardiac death.

General to DCMs, a high burden of VPCs can sometimes be observed. There is often ambiguity around whether the frequent VPCs result from the underlying cardiomyopathy or are a driver of the cardiomyopathy. The near eradication of VPCs in this patient was initially attributed to amiodarone therapy; however, given the continued absence of frequent VPCs after long-term discontinuation of the drug, it seems likely due to a decrease in left ventricular volumes, withdrawal from heavy running, or a combination of these factors. Acquired factors like pregnancy, cardiotoxic chemotherapy or excess alcohol consumption are known to modify the phenotypic manifestations of *TTN* gene pathogenic variants [4-6]. Left ventricular mass is lower in *TTN*tv DCM than in idiopathic DCM of similar severity [10,11]. Running 20 miles to 25 miles per week for 20 years is likely to have partly contributed to the left ventricular remodeling/dilatation in our patient. In turn, left ventricular dilatation may have exacerbated electrical and mechanical left ventricular alterations in a patient who, with *TTN*tv, may not have been able to develop adequate compensatory left ventricular hypertrophy and normalize left ventricular stress.

Conclusions

The understanding and identification of *TTN* gene mutations and their specific cardiac phenotypes is still a work in progress.

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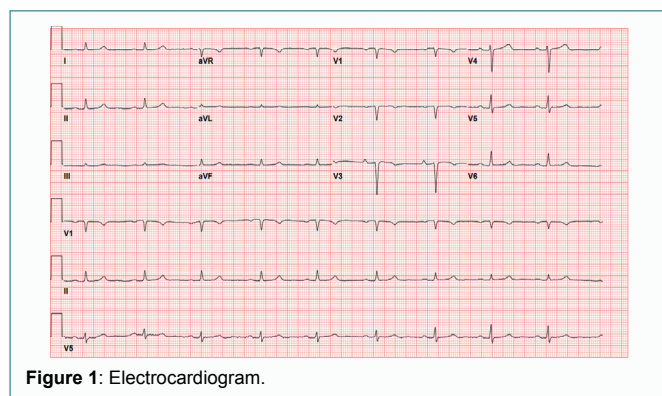


Figure 1: Electrocardiogram.

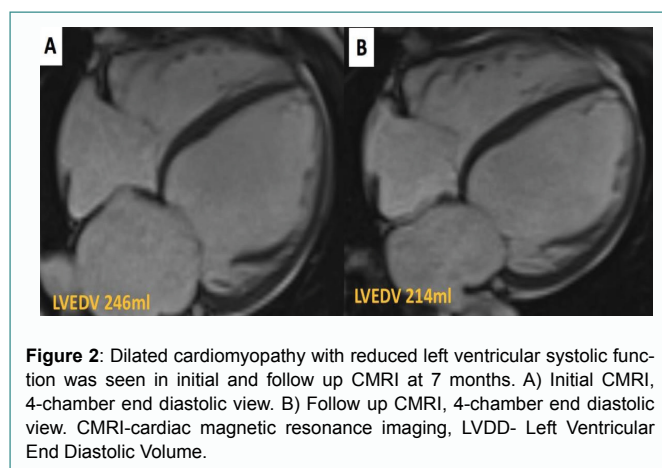


Figure 2: Dilated cardiomyopathy with reduced left ventricular systolic function was seen in initial and follow up CMRI at 7 months. A) Initial CMRI, 4-chamber end diastolic view. B) Follow up CMRI, 4-chamber end diastolic view. CMRI-cardiac magnetic resonance imaging, LVDD- Left Ventricular End Diastolic Volume.

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