Familial Left Ventricular Noncompaction And Conduction Abnormalities. A Case Report with Genetic Mutation

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Abstract

Background: Left Ventricular Noncompaction (LVNC) is a rare form of cardiomyopathy resulting from arrest in the normal endomyocardial compaction, characterized by the presence of prominent trabeculations and deep intertrabecular recesses. Clinical manifestations range from being asymptomatic, heart failure, arrhythmia and thromboembolism. Atrioventricular block (AV) block is a rare presentation.

Materials and Methods: In a patient presented with complete heart block and LVNC genomic DNA of thirteen genes associated with LVNC was analyzed by sequencing for exons, splicing and flanking regions. Novel variants were confirmed by independent Sanger sequencing. A novel variant in the Myosin Heavy Chain 7 gene (MHC7) was identified, alongside with two other variants in the (MHC7) and Vinculin (VCL).

Conclusion: The Genetic basis association between LVNC and heart block has been rarely reported, here we review the literature of similarly published cases.

Keywords: Non-compaction; Myosin; Heart block; Genetics

Introduction

Left Ventricular non-compaction (LVNC) is a rare disorder affecting the morphogenesis of the endomyocardium manifesting as multiple trabeculations in the ventricular myocardium [1]. Its clinical manifestations range from being asymptomatic, congestive heart failure, ventricular arrhythmias or thromboembolic manifestations [1,2]. The association between LVNC and conduction abnormalities has been extremely uncommon. Our case presented with complete heart block and ventricular noncompaction.

Learning objectives

• Understand the nature of the rare form of cardiomyopathy (non-compaction)
• To know the uncommon association with heart block
• The role of genetic mutation in this form of cardiomyopathy
• The importance of family screening

Case Report

A 34-year-old male farmer patient presented with Progression of his baseline dyspnea New York Heart Association (NYHA) class II to IV and dizziness. He was previously diagnosed with congestive heart failure and was maintained on angiotensin converting enzyme inhibitor (ACEi) and diuretics.

On admission, his heart rate was 30 Bpm, BP: 90/60 mmHg, elevated neck venous pressures, No LL edema.

His ECG showed complete heart block with ventricular escape rate 27 Bpm (Figure 1 panel A).

Echocardiography: dilated left ventricle, hypertrabeculation with deep recesses seen in the apex, apical and middle part of the lateral and inferoposterior walls with reduced systolic function, EF:45% (Figure 1 panel B).

The ratio of noncompacted to compacted myocardium was >2 in the maximal thickened wall, measured at the end systole. On color Doppler echocardiography, these recesses were filled with blood from the ventricular cavity.

Neurological examination was free. His laboratory investigations were normal.

A pacemaker was implanted and his symptoms markedly improved on discharge and on follow-up visit.

After their consent, screening (clinical, electrocardiographic and echocardiographic) of family members revealed the following (Figure 1 panel C).

Sister 1 was 31-year-old complaining of dyspnea NYHA class III, orthopnea and bilateral lower limb swelling. A systolic murmur grade III/IV was heard over the apex, her pulse was irregular; 90 Bpm, elevated jugular pressure with mild ankle edema.

ECG: Atrial fibrillation on 100 Bpm with left bundle branch block (Figure 2 panel A).

Figure 1: Index patient panel A: ECG showing complete heart block. Panel B: Echocardiography showing non-compaction. Panel C: Family pedigree.

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The diagnosis was subsequently confirmed by cardiac MRI which showed also hypertrabeculation with deep recesses along with biastral dilatation. Sister 2 was 33-year-old, complaining of exertional dyspnea NYHA class II. S3 gallop was heard.

ECG: sinus rhythm, P mitral, RBBB morphology, 70 Bpm (Figure 3 panel A, Figure 4, Video 1)

Echocardiography: Hypertrabeculations and deep recesses seen in apical, mid-cavity of the lateral and posterior wall. LVEF: 65%, no valvular affection (Figure 3 panel B).

Materials and Methods

Mutations in 13 genes (ACTC1, CASQ2, DTNA, LDB3, LMNA, MIB1, MYBPC3, MYH7, PRDM16, TAZ, TNNT2, TPM1, VCL) have been associated with LVNC.

His genomic DNA was analyzed by sequencing for exons, splice junctions and flanking regions of the previously mentioned genes. Test was performed by oligonucleotide-based target capture (SeqCap EZ, NimbleGen) followed by NGS (MiSeq, Illumina). Clinically significant and novel variants are usually confirmed by independent Sanger sequencing. DNA sequence is assembled to and analyzed in comparison with the genomic reference sequences published in the NCBI database to generate variant calls.

This test was developed and its performance characteristics determined by the John Welsh Cardiovascular Diagnostic Laboratory. This sequence analysis identified two missense heterozygous variants c.1189A>G (p.Lys397Glu) and c.3469A>G (p.Thr1157Ala) in the MYH7 gene (OMIM 160760) and one missense heterozygous variant c.1917G>T (p.Lys639Asn) in the VCL gene (OMIM 611407). The MYH7 variant c.1189A>G (p.Lys397Glu) has not been reported before, whereas the other MYH7 variant c.1917G>T (p.Lys639Asn) has been seen in the dbSNP database with accession #rs730880775. However, the VCL variant c.1917G>T (p.Lys639Asn) has been previously reported in the ExAC database (http://exac.broadinstitute.org/) with minor allele frequency (MAF (%)) 0.0008295. All three variants identified in both MYH7 and VCL genes in this individual were predicted to be damaging by computational analysis.

Results and Discussion

Development

During the development of the heart; myocardial maturation undergoes complex changes during development, those changes could be grouped into four steps: (i) early heart tube, (ii) emergence of trabeculations, (iii) trabecular remodeling, (iv) development of the multilayered spiral system [3-5].

Emergence of trabeculations occurs at the 4th week of gestation and their remodeling starts after completing the ventricular septation, at the 8th gestational week. Papillary muscles of the mitral valve are formed by the union of some of the luminal trabeculations whereas apical trabeculations transform into fine honeycomb-like reliefs on the inner ventricular surface. The sequence of compaction starts from the epicardium to the endocardium, from the septum to the free wall and from the base to the apex of the left ventricle [3].

Echocardiographic diagnosis

Echocardiography is the most widely used method of diagnosis of LVNC, several diagnostic criteria have been proposed; Jenni et al. proposed a ratio of noncompacted: compacted myocardium >2 measures

Echocardiography: Left ventricular noncompaction, hypertrabeculation in the apex and mid-cavity mainly in the lateral wall, biastral dilatation, EF: 50%, moderate mitral regurgitation and mild tricuspid regurgitation (Figure 2 panel B).

Figure 2: Sister 1 Panel A: ECG showing atrial fibrillation and left bundle branch block. Panel B: Echocardiography showing bilateral dilatation and left ventricular non-compaction.

Figure 3: Sister 2 Panel A: ECG showing right bundle branch block. Panel B: Echocardiography showing left ventricular non-compaction.

Figure 4: Cardiac MRI of sister 1 showing hypertrabeculation and deep interventricular recesses.
in short-axis at end systole [6]. However, Stöllberger et al. considered the presence of more than 3 coarse and prominent trabeculations, moving synchronously with the myocardium having the same echogenicity and are surrounded by intertrabecular spaces to be diagnostic of LVNC [7].

Finsterer and Stöllberger proposed a new definition categorizing echocardiographic findings into definite, probable and possible NCVM. Depending on the two old definitions; LVNC is definitely present if the two old criteria are present, the diagnosis is probable if only one criterion is present and possible LVNC is present if either the number of trabeculations is less than 3 or if the ratio of noncompacted to compacted LV<2 [8]. Other imaging modalities like cardiac magnetic resonance, strain rate and speckle tracking have been described as well.

Genetics and conduction abnormalities
LVNC commonly presents with heart failure, arrhythmia and thromboembolic manifestations, however it may rarely present with conduction deficits [9]. It has been rarely reported in adults; however, in a pediatric series advanced AV block (2nd and 3rd degree) was reported in three out of 27 patients with LVNC. Loss of function of hNav 1.5 by a ZASP1 mutation is associated with interventricular conduction disturbance in LVNC [10]. Several cases of LVNC and conduction abnormalities were reported [1,8,9,11-15]. Familial occurrence has been reported by Taniguchi et al. where LVNC and conduction block were found in two siblings of the indexed patient [12]. Vinculin is one of the components of the intercalated discs as well as costameres; structures anchoring the thin filaments and transmits contractile force between cardiac myocytes [16,17]. Mutations in Vinculin have been rarely associated with dilated cardiomyopathy in humans [17,18].

Conduction abnormalities are not always present in humans [17]. Mice with Vin
culin mutations were reported to die suddenly [19-21]. The exact mechanism by which conduction deficit occurs in LVNC is not known, but it is postulated that fibrosis play a role in the occurrence and progression of conduction abnormalities in LVNC. Our case met the echocardiographic criteria of diagnosis of LVNC and received VVI pacemaker as a management of heart block. His siblings will undergo follow up every 3 months to define the proper time of intervention.

Conclusion
In the light of the previous data; ventricular noncompaction may rarely present with conduction deficit, which should be kept in mind during initial assessment and follow-up. Vinculin gene mutations need further research. Family screening is advised using electrocardiography and echocardiography. Further research to identify genes implicated in association between ventricular non-compaction and conduction deficits is needed with special emphasis on vinculin mutations.

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