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Case Report

RBM20 mutation and ventricular arrhythmias in a young patient with dilated cardiomyopathy: a case report

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Abstract: Gene mutations in RBM20 have been identified in a minority of familial and sporadic dilated cardiomyopathy cases. Recent studies of carriers of RBM20 mutations not only highlight the aforementioned association with dilated cardiomyopathy but also indicate a link with increased incidence of ventricular arrhythmias. Herein we describe a case of 17-year-old female patient with dilated cardiomyopathy carrying a p.(Arg634Trp) RBM20 mutation and presenting with frequent premature ventricular contractions and episodes of non-sustained ventricular tachycardia.

Keywords: RBM20 gene, cardiomyopathy, ventricular arrhythmias, mutation

Background

Dilated cardiomyopathy (DCM) is defined as left ventricular (LV) dilation and systolic dysfunction in the absence of coronary artery disease or abnormal loading conditions. The prevalence of dilated cardiomyopathy, which is one of the leading causes of heart failure (HF), is estimated at up to 1 in 250 of the population. DCM can result from a diverse range of etiologies including complex interactions between the environment and genetic predisposition. The above mentioned factors can lead to adverse remodelling, which is characterised by progressive left and often right ventricular dilatation, impairment of systolic function and accompanying myocardial fibrosis. The mortality rates appear relatively high, despite advances in heart failure treatment. Death may result from heart failure progression and malignant ventricular arrhythmias. Until now more than 50 genes have been associated with the condition [1]. In this article we describe a patient with dilated cardiomyopathy carrying a p.(Arg634Trp) RBM20 mutation and presenting with episodes of non-sustained ventricular tachycardia (NSVT).

Case presentation

A 17-year-old female referred to our hospital due to ventricular arrhythmias combined with a dilated cardiomyopathy (DCM) phenotype. Her past medical history was remarkable for lymphoma/B-cell leukemia (diagnosed in 2006 and treated by chemotherapy regimens until 2008). No family history of sudden cardiac death was reported. Her mother was also diagnosed with DCM a year ago and underwent ICD implantation.

Investigations

Our patient's resting electrocardiogram (ECG) demonstrated sinus rhythm, frequent premature ventricular contractions (PVCs), presenting with a left bundle branch block (LBBB)-inferior axis morphology (**Figure 1**). An echocardiogram was performed and demonstrated left ventricular (LV) dilation combined with moderate LV sys-

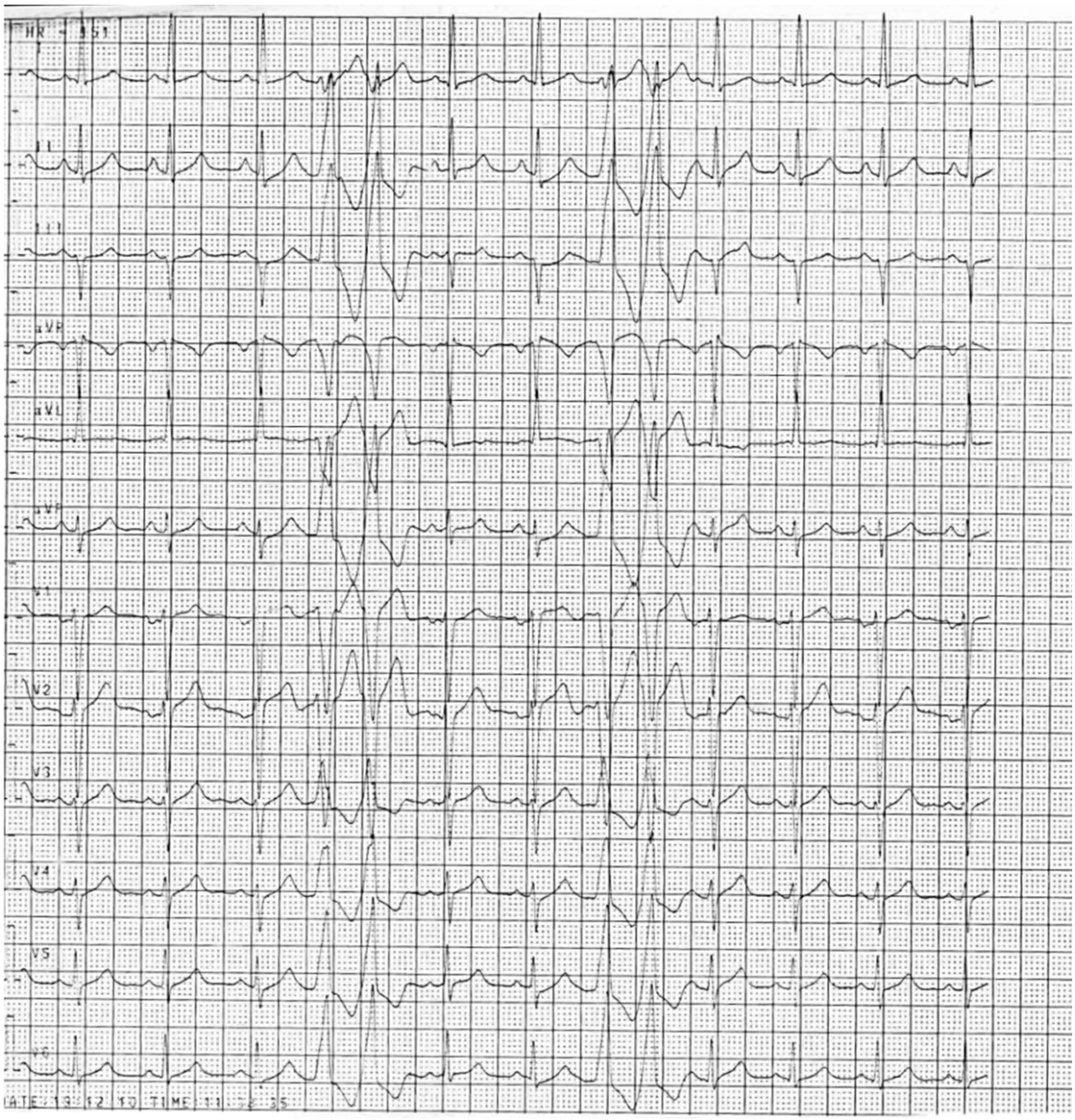

Figure 1. 12-lead ECG demonstrating sinus rhythm with couplets of premature ventricular contractions (PVCs) with left bundle branch block (LBBB)-inferior axis morphology.

tolic dysfunction. In addition, the patient underwent a 12-lead 24-h Holter monitoring which revealed 10.300 premature ventricular contractions. Among them, some episodes of non-sustained ventricular tachycardia (NSVT) were recorded. She also underwent signal averaged ECG (SAECG), where total QRS Duration (filtered), RMS Voltage in terminal 40 msec as well as duration HFLA signals were all found negative. Cardiac magnetic resonance imaging (CMR) showed no evidence of myocardial scarring/necrosis or fibrosis. Electrophysiologic study (EPS) and catheter ablation procedure were proposed in order to minimise PVCs' burden. After informed written consent had been obtained, EPS was carried out. Activation mapping revealed the earliest activation site at the left pulmonary cusp. Radiofrequency energy delivery abolished the PVCs. Programmed ventricular stimulation did not induce sustained ventricular arrhythmia. The patient was further referred for genetic testing.

Genetic test

The genetic basis of the disease was identified for the proband with Next Generation Sequencing technology, using Sophia Extended

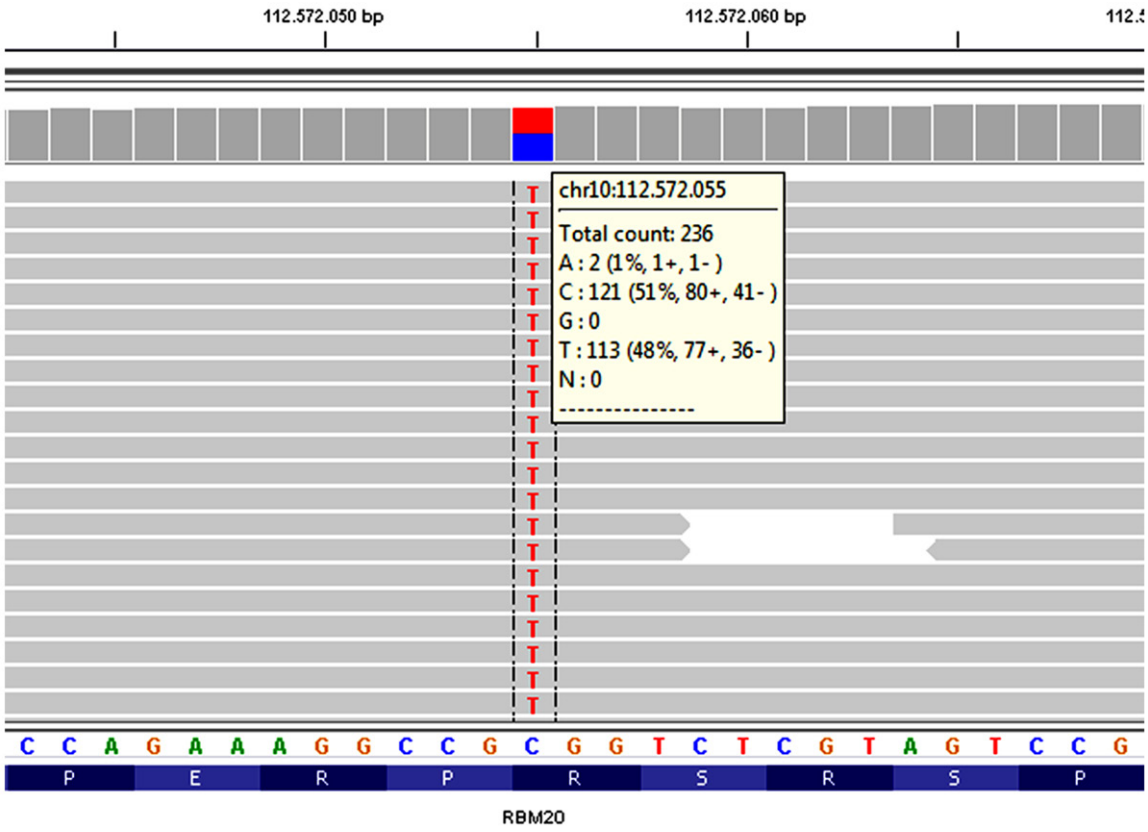

Figure 2. IGV snapshot of c.1900C > T variant in the *RBM20* gene (Chr 10:112572055, hg19).

Cardio Solution (Sophia Genetics) on the Illumina NextSeq platform according to manufacturers' instructions. Alignment, quality filtering, variant calling, and variant annotation were performed using the Sophia Genetics pipeline. The variant calling files were filtered using the Sophia Genetics DDM platform, whereas the detected variants were characterized according to the recommendations of the American College of Medical Genetics and Genomics (ACMG) [2]. All benign or likely benign variants were filtered out and the retained variants were subsequently evaluated according to the relevance of the gene to the observed phenotype. The sample of the proband was sequenced with a mean target region coverage depth of 165× and 100% of the target region was covered at a minimum depth of 25×.

The proband was found to carry an heterozygous variant in the RBM20 gene: NC_000010.10:g.112572055C > T, NM_001134363.2:c.1900C > T, p.(Arg634Trp) (**Figure 2**) which was subsequently confirmed by Sanger sequencing. The variant was absent from the Genome Aggregation Database but has been reported in ClinVar (rs796734066) as likely pathogenic/pathogenic by three submitters. Pathogenicity algorithms predicted a damaging effect of this amino acid substitution (SIFT: 0, PolyPhen-2 HumVar: 1.000, Mutation Taster: 0.973 and DANN: 0,9959), since the variant affected a highly conserved amino acid (Consurf: 9) and at the same codon position the alternative p.(Arg634Gln) amino acid substitution has been characterized as pathogenic [3, 4]. The mutation was located in a region that is required for nuclear localization of RBM20 [5] and *in vitro* functional assays showed that mutations in this region disturb RBM20 localization to the nucleus, where the protein exerts its physiological function [6].

Follow up and outcomes

Echocardiographic follow-up demonstrated left ventricular (LV) dilation combined with moderate to severe LV systolic dysfunction. 12-lead 24-h Holter monitoring revealed again frequent premature ventricular contractions. Among th-

em, some episodes of non-sustained ventricular tachycardia (NSVT) were again recorded. A second Electrophysiologic study (EPS) and catheter ablation procedure were proposed in order to minimise PVCs' burden. After informed written consent had been obtained, second EPS was carried out. Activation mapping revealed the earliest activation site at the right/left coronary cusp commissure. Radiofrequency energy delivery did not abolish the PVCs. Due to the above mentioned aggressive arrhythmogenic phenotype (despite maximum tolerated antiarrhythmic therapy) and the worsening LV function, an implantable cardioverter-defibrillator (ICD) implantation was advised. The risks, benefits, and alternative of the procedure were all discussed with the patient including the risk of inappropriate ICD shocks. She agreed to the procedure, and informed consent was obtained. She finally underwent ICD implantation.

Discussion

Encoding RNA Binding Motif Protein-20 (RBM20) is a RNA-binding protein consisting of one RNA-recognition motif (RRM) domain and two zinc finger (ZnF) domains [7]. RBM20 gene has already been identified as one of the DCM-associated genes [3]. Genetic alterations in RBM20 have been observed in 2-3% of familial and sporadic DCM cases [8-10]. Recently, RBM20 was identified to play an important role as a crucial regulator of the splicing of titin (TTN) [11], a high-molecular-weight protein that provides passive stiffness to the sarcomere. Therefore, a primary molecular mechanism attributed to RBM20 mutations was suggested as a change in TTN isoforms, resulting in adverse cardiac remodeling and DCM development. Currently, over 20 genes have been shown to be a target of RBM20, including TRDN, RYR2, CACNA1C, RTN4, FHOD3, PDLIM3, OBSCN, and many others [11-15].

A recent study of carriers of RBM20 gene mutations identified not only the aforementioned association with DCM but also with increased incidence of ventricular arrhythmias (VAs) [16]. Despite similar LVEF.%, approximately 44% of RBM20 mutation carriers presented with sustained VAs compared to only 5% of TTN mutation carriers. In another multicentre study, among 74 RBM20 mutation carriers, family history of SCD was reported in 51% of patients. Furthermore, patients with RBM20 mutations were more likely to have NSVT (43% vs 11%) and sustained VT (25% vs 2%) than idiopathic DCM cohorts [17]. Of note, Vakhrushev et al. recently presented a clinical case of a rare arrhythmogenic phenotype (several syncope and NSVT episodes with no response to antiarrhythmic drugs) and no structural cardiac abnormalities associated with a RBM20 genetic variant of uncertain significance (VUS), thus underlining the potentially malignant character of such mutations [18].

RBM20 cardiomyopathy also appears to present in a more severe fashion in male patients: In a study which included 80 RBM20 mutation carriers, men were both younger at the time of diagnosis and presented with a lower ejection fraction ("age, 29 ± 11 versus 48 ± 12 years; $P < 0.01$; ejection fraction, 29 ± 13% versus 38 ± 9%; $P < 0.01$"). One-third of male patients finally required a heart transplant (aged 33 ± 16 years old), whereas none of the female patients required the procedure. Male patients also appeared to have a significantly lower total event-free survival compared with female patients. Interestingly, male RBM20 cardiomyopathy patients also fared worse when compared to a cohort of DCM patients of unknown genetic cause, while female RBM20 cardiomyopathy patients showed better event-free survival when compared to DCM patients of unknown cause, thus suggesting that the observed sex differences are not shared by all forms of DCM, but rather (at least to some degree) specific to RBM20 cardiomyopathy [19].

Conclusion

Our proband was diagnosed carrying a p.(Arg634Trp) RBM20 mutation, which is linked to a clinically aggressive form of DCM. This may include severe heart failure, increased arrhythmogenic risk, and the need for a cardiac transplantation procedure at a younger age compared to sporadic DCM cases, suggesting that this may be an important cause of familial DCM. However, its precise frequency and exact pathophysiological role still remains to be elucidated. Most importantly, closer study of the described families reveals that penetrance may be variable and variations in other DCM related genes can be found as well. Given the suggested arrhythmogenic malignancy of

RBM20 mutations, identifying such mutations should probably suggest careful attention to coexistent modifiable risk factors, a closer clinical follow up, and finally an earlier application of therapies proven to inhibit the process of heart failure and decrease the risk of sudden cardiac death.

Acknowledgements

All procedures performed in our study were in accordance with the ethical standards of the institutional and the national research committee at which they were conducted (IRB approval number 2012180000008) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Disclosure of conflict of interest

None.

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