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Case Report

Co-existence of RBM20 and KCNQ1 gene mutations in a patient with long QT syndrome and dilated cardiomyopathy. "Which came first: Chicken or the egg?"

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ABSTRACT

A 60-year-old female patient was taken to the emergency department with a history of syncope. ECG revealed polymorphic ventricular tachycardia which necessitated recurrent DC cardioversion. Post-reversion ECG showed sinus rhythm with prolonged corrected QTc. Bedside transthoracic echocardiogram revealed features suggestive of dilated cardiomyopathy (DCM) with severe left ventricular dysfunction. Next reversion to VT was managed with intravenous propranolol and DC cardioversion after which she remained in sinus rhythm. After the initiation of beta-blocker, she developed sinus bradycardia followed by complete heart block.

The concern we had while managing this case was whether the DCM caused the VT {then why long QTc?} OR was the long QTc causing DCM {due to same gene mutation}. Genetic analysis revealed the simultaneous occurrence of KCNQ1 and RBM20 mutation.

Regarding the treatment given to our patient, we continued beta-blocker, left bundle branch optimized implantable cardioverter defibrillator {LOT – Dx ICD} was done with atrial sensing, the right ventricular coil as the defibrillator, and left bundle branch area pacing.

In our patient, any of the two mutations could explain the occurrence of both DCM and long QTc. However genetic analysis revealed the simultaneous presence of both RBM20 and KCNQ1 mutation. To the best of our knowledge, this is the first report in the medical literature on the co-existence of RBM20 and KCNQ1 mutation.

1. Introduction

Congenital long QT syndrome (LQTS) is an inherited cardiac channelopathy characterized by prolongation of the QT interval on electrocardiogram (ECG). It is associated with an increased risk of life-threatening ventricular arrhythmias. The pathogenesis of LQTS has been tied up with mutations in more than a dozen different genes [1]. A heterozygous loss-of-function mutation in the KCNQ1 gene, which codes for the α-subunit of the delayed rectifier inward potassium ion channel, is the hallmark of LQTS type 1 (LQT1), the most frequent LQTS variant.

One recognized cause of dilated cardiomyopathy (DCM) is mutations in the gene encoding RNA-binding motif protein 20 (RBM20). Since RBM20 is responsible for around 3 % of instances of familial DCM, disease-causing mutations in this gene are very common in familial DCM. A clinically aggressive type of DCM, characterized by early diagnostic age, rapid heart failure progression, elevated arrhythmia risk, and high mortality, is reported to manifest in carriers of the RBM20 mutation [2].

2. Case report

A 60-year-old female patient was taken to the emergency department with a history of syncope. On presentation, she was hypotensive with ECG revealing polymorphic ventricular tachycardia (VT) (Fig. 1). She underwent DC cardioversion and reverted to sinus rhythm. But soon VT recurred and repeated DC cardioversions were needed. Post-cardioversion ECG revealed sinus rhythm with prolonged corrected QTc (511 milliseconds by Bazett formula) (Fig. 2). Next episode of VT was managed with intravenous propranolol (1 mg) and DC cardioversion after which she remained in sinus rhythm. Bedside transthoracic echocardiogram revealed features suggestive of dilated cardiomyopathy (DCM) with severe left ventricular dysfunction {Left ventricular end-diastolic dimension – 60 mm and left ventricular ejection fraction - 28 % by Simpson's method}. Routine investigations showed normal

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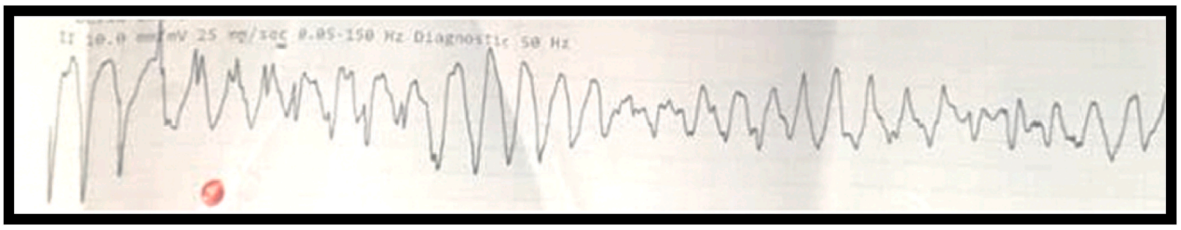

Fig. 1. ECG rhythm strip on presentation showing polymorphic VT.

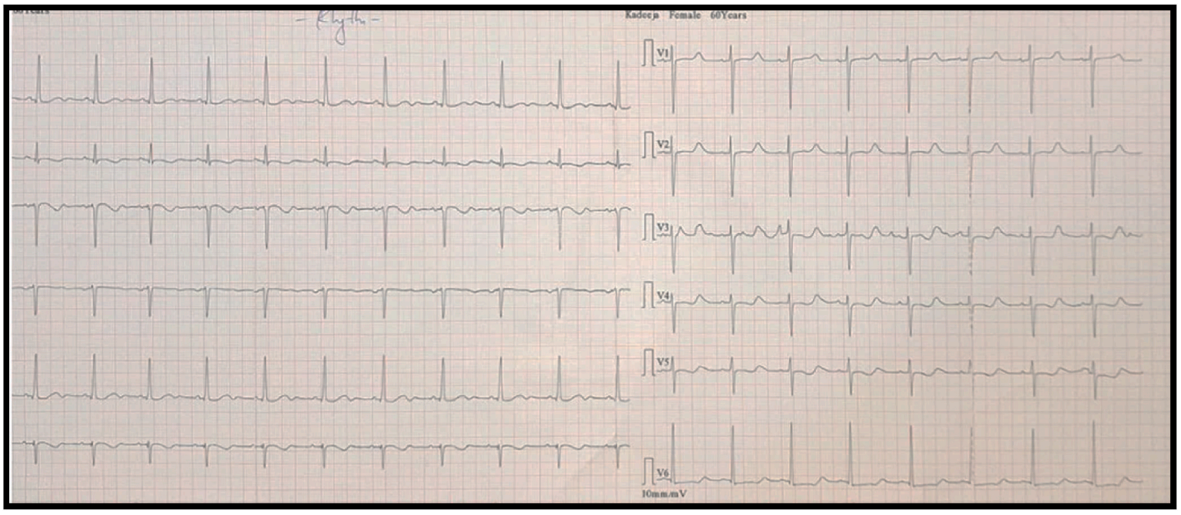

Fig. 2. ECG after DC cardioversion showing sinus rhythm with long QTc.

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance
***RBM20* (+)** (ENST00000369519.4)	Exon 9	c.1906C>T **(p.Arg636Cys)**	Heterozygous	Dilated cardiomyopathy-1DD (OMIM#613172)	Autosomal dominant
***KCNQ1* (+)** (ENST00000155840.12)	Exon 11	c.1456G>A **(p.Ala486Thr)**	Heterozygous	Long QT syndrome-1 (OMIM#192500)	Autosomal dominant

Fig. 3. Genetic analysis report showing the presence of both RBM 20 and KCNQ1 mutation.

levels of electrolytes and thyroid hormones. There was no history suggestive of significant cardiovascular illness or sudden death in the family.

After the initiation of beta-blocker, she developed sinus bradycardia followed by complete heart block for that she was put on a transvenous temporary pacemaker and beta-blocker was withdrawn.

Our concern while managing this case was whether the DCM caused the VT {then why long QTc?} OR was the long QTc causing DCM {due to same gene mutation}.

The options of management that we made for this patient were (a) cardiac resynchronization therapy with a defibrillator (CRT-D) {which the patient was not affording}, (b) permanent pacemaker – Left bundle area pacing/Implantable cardioverter defibrillator and continuing propranolol {as the patient was not tolerating betablocker}.

By this time, genetic analysis report was obtained (Fig. 3) which revealed the simultaneous occurrence of KCNQ1 and RBM20 mutation.

Regarding the treatment given to our patient, we continued beta-blocker, left bundle branch optimized implantable cardioverter defibrillator {LOT – Dx ICD with DF1 device} was done with atrial sensing, the right ventricular coil as the defibrillator, and left bundle branch area pacing (Fig. 4). There were no periprocedural complications. The patient was discharged on day 5 in a stable state and is on regular follow-up.

3. Discussion

In addition to DCM, patients with RBM20 mutations frequently have cardiac arrhythmias. Numerous essential cardiac genes, including CAMK2D (calcium/calmodulin-dependent kinase II delta) and Titin (TTN), are targeted by the splicing factor RBM20 [3]. Although aberrant TTN splicing is believed to be the primary cause of RBM20-induced dilated cardiomyopathy, it is unlikely to account for the elevated risk of arrhythmias. An increase in intracellular Ca2+ overload, higher sarcoplasmic reticulum Ca2+ content, increased spontaneous Ca2+ releases, and an enhanced L-type Ca2+ current density are all brought on by RBM20 loss [2]. The elevated risk of arrhythmias in carriers of RBM20 mutations is caused by this disrupted Ca2+ handling brought on by malfunctioning RBM20. In our case instance, the RBM20 mutation can explain the patient's DCM and ventricular tachycardia. However, the presence of long QTc and KCNQ1 mutation continues to be

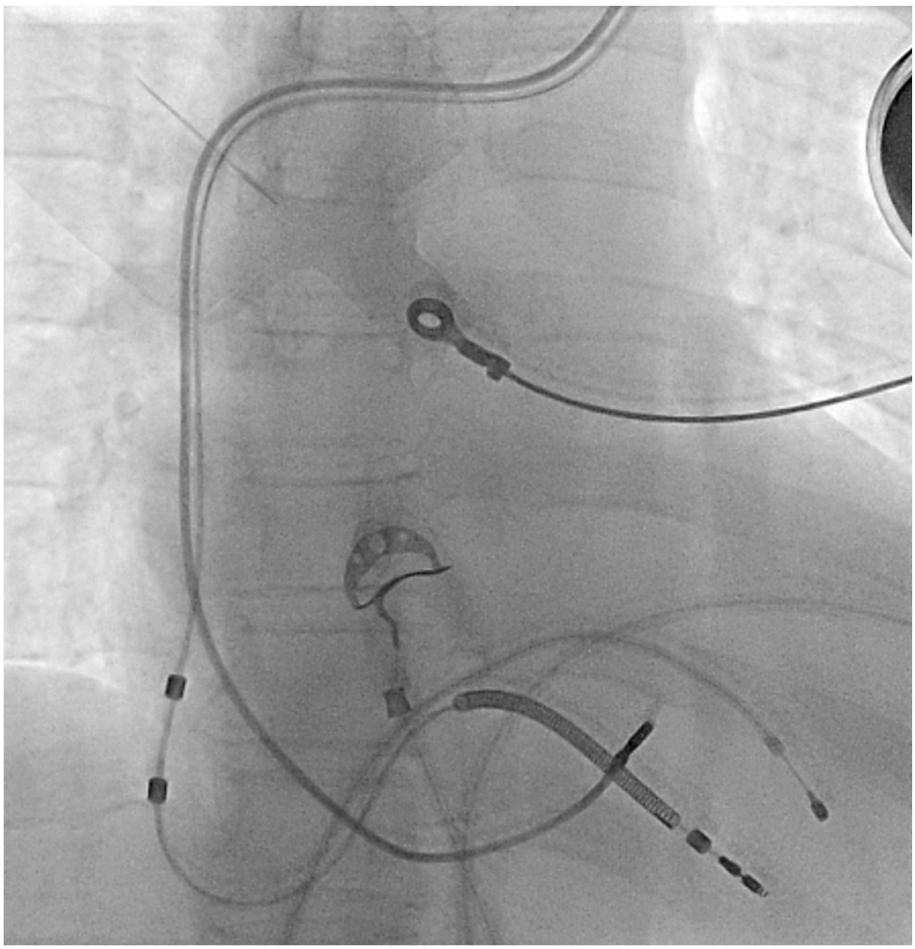

Fig. 4. Showing LOT – Dx ICD with DF1 device with atrial sensing, the right ventricular coil as the defibrillator, and left bundle branch area pacing.

unexplained.

The prototype for cardiac ion channel disorders that result in syncope and sudden death is Long QT syndrome (LQTS). KCNQ1 mutations cause LQT1 (KVLQT1), which is the most prevalent type. While a cardiac sodium channel "overlap syndrome" between channelopathies and cardiomyopathies has been described related to abnormalities in the SCN5A gene (LQTS 3), no such association with DCM has been described with respect to the cardiac potassium channels involved in LQT1. LQTS type 3 (LQT3), Brugada syndrome, sick sinus syndrome, conduction system disease, sudden infant death syndrome, and DCM are among the pathologic cardiac disorders attributed to the SCN5A gene, which encodes the α-subunit of the voltage-dependent cardiac sodium channel [4]. Our patient carried genotypic and phenotypic characteristics of LQT1 and went on to develop DCM without evidence of frequent ventricular ectopic beats or sustained arrhythmias, making a tachycardia- or PVC-induced cardiomyopathy unlikely.

In their multicenter cohort of 338 DCM patients, McNair et al. [5] discovered a 1.7 % prevalence of SCN5A mutations. While none of these patients had QTc prolongation, multiple case reports have described an overlap between ECG evidence of LQTS and DCM in patients with mutations in the SCN5A gene. The mechanism of overlap between channelopathy and cardiomyopathy in LQT3 is not well understood, but it has been proposed that ion channel mutations may ultimately result in structural changes to the myocardial tissue via their interaction with cytoskeletal proteins, either directly or as a result of altered ion homeostasis [6].

Although KCNQ1 gene mutations have been linked to other cardiomyopathies such as hypertrophic cardiomyopathy and LV noncompaction cardiomyopathy, they have not yet been identified in patients with DCM. The delayed rectifier potassium channel affected in LQT1 is one of several types of potassium channels responsible for reconstitution of the cardiac action potential, whereas the function of the SCN5A channel is absolutely necessary for depolarization and, hence, contractile function [7,8]. It may be that, unlike sodium channel mutations, a single potassium channel mutation is insufficient to cause a significant effect on contractile function without additional abnormalities in cytoskeletal proteins or cardiac metabolism.

According to a study of 80 carriers of pathogenic DNA-sequence variants in the gene for RBM20 [9], 60 % of all male RBM20 carriers experienced a major cardiovascular event before the age of 40 years, while this happened in $<$5 % of females. Only male carriers had end-stage heart failure, necessitating cardiac transplantation. The severe disease expression in carriers of pathogenic RBM20-variants suggested that close clinical follow-up of affected and unaffected individuals is warranted to ensure adequate and timely treatment.

Family members of individuals with established LQTS frequently lack unequivocal clinical signs, but may have inherited an LQTS mutation and are at risk of sudden death. Genetic testing can identify mutations in 75 % of patients with LQTS, but genetic testing of family members remains controversial. A Schwartz score of $\geq$3.5 in family members is highly specific, but not sensitive for identifying LQTS.

4. Conclusion

Although a mutation in KCNQ1 has not yet been identified as the cause of DCM, potassium ion channels may play a role in the pathophysiology of myocardial dilatation and ventricular dysfunction. The function of the delayed rectifier potassium channel in heart failure has

not received much attention.

Despite having comparably impaired left ventricular function, individuals with a pathogenic RBM20 mutation have more ventricular arrhythmias than patients with a Titin mutation. Even in the early stages of the disease, bearers of the RBM20 mutation should be constantly watched for possible cardiac arrhythmias and electrical abnormalities. To lessen their burden of arrhythmias, bearers of the RBM20 mutation can benefit from therapy with an L-type Ca2+ current blocker.

In our patient, any of the two mutations could explain the occurrence of both DCM and long QTc. However genetic analysis revealed the simultaneous presence of both RBM20 and KCNQ1 mutation. To the best of our knowledge, this is the first report in the medical literature on the co-existence of RBM20 and KCNQ1 mutation.

Consent

The authors confirm that written consent had been obtained from the patient and his relatives for using the images, and clinical details and for submission as a case report in the journal. The patient and her relatives understand that their names and initials will not be published and that due efforts will be made to conceal their identity.

Key messages

Long QT syndrome and dilated cardiomyopathy have previously been linked in the presence of SCN5A mutations, suggesting a sodium channel “overlap syndrome".

Although a mutation in KCNQ1 has not yet been identified as the cause of DCM, potassium ion channels may play a role in the pathophysiology of myocardial dilatation and ventricular dysfunction.

Additional cardiomyopathy screening may be necessary in patients with a variety of hereditary channelopathies.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Giudicessi JR, Ackerman MJ. Genotype- and phenotype-guided management of congenital long QT syndrome. Curr Probl Cardiol 2013 Oct;38(10):417–55.
[2] Van Den Hoogenhof MMG, Beqqali A, Amin AS, Van Der Made I, Aufiero S, Khan MAF, et al. RBM20 mutations induce an arrhythmogenic dilated cardiomyopathy related to disturbed calcium handling. Circulation 2018 Sep 25;138 (13):1330–42.
[3] Guo W, Schafer S, Greaser ML, Radke MH, Liss M, Govindarajan T, et al. RBM20, a gene for hereditary cardiomyopathy, regulates titin splicing. Nat Med 2012 May;18 (5):766–73.
[4] Wilde AAM, Amin AS. Clinical spectrum of SCN5A mutations. JACC Clin Electrophysiol. 2018 May;4(5):569–79.
[5] McNair WP, Sinagra G, Taylor MRG, Di Lenarda A, Ferguson DA, Salcedo EE, et al. SCN5A mutations associate with arrhythmic dilated cardiomyopathy and commonly localize to the voltage-sensing mechanism. J Am Coll Cardiol 2011 May;57(21): 2160–8.
[6] Remme CA. Cardiac sodium channelopathy associated with *SCN5A* mutations: electrophysiological, molecular and genetic aspects. J Physiol 2013 Sep;591(17): 4099–116.
[7] Giudicessi JR, Ackerman MJ. Potassium-channel mutations and cardiac arrhythmias—diagnosis and therapy. Nat Rev Cardiol 2012 Jun;9(6):319–32.
[8] Liu M, Yang KC, Dudley SC. Cardiac sodium channel mutations: why so many phenotypes? Nat Rev Cardiol 2014 Oct;11(10):607–15.
[9] Hey TM, Rasmussen TB, Madsen T, Aagaard MM, Harbo M, Mølgaard H, et al. Pathogenic *RBM20* -variants are associated with a severe disease expression in male patients with dilated cardiomyopathy. Circ Heart Fail 2019 Mar;12(3):e005700.