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A 59-Year-Old Woman with Familial Brugada Syndrome and the c.664C>T Variant of the Sodium Voltage-Gated Channel Alpha Subunit 5 (SCN5A) Gene, Accompanied by Congenital Absence of the Right Coronary Artery, Patent Foramen Ovale, and Ischemic Stroke

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 59-year-old
Final Diagnosis: Absence of right coronary artery • patent foramen ovale • positive for Brugada-related gene variant
Symptoms: Angina
Medication: —
Clinical Procedure: —
Specialty: Cardiology

Objective: Rare coexistence of disease or pathology

Background: Brugada syndrome is a rare inherited channelopathy that can lead to sudden cardiac death. The discovery of new variants of variable penetrance along with the current guidance for cascade family screening can be expected to lead to an increase in identified asymptomatic carriers of potentially causative mutations of channelopathies. A single coronary artery is a rare congenital anomaly of the coronary anatomy. We present a rare case of a 59-year-old woman with a family history of Brugada syndrome with the c.664C>T variant of the SCN5A gene, congenital absence of the right coronary artery, and patent foramen ovale.

Case Report: We present a case of a patient with a family history of Brugada syndrome who tested positive for the SCN5A variant. The patient had no previous history of syncope or aborted sudden cardiac death. The patient had no features suggestive of Brugada type I ECG. An electrophysiology study was offered but the patient declined. She also complained of angina, and work-up with computed tomography coronary angiography revealed a congenital absence of the right coronary artery with no significant stenosis of the single left coronary artery. In the followup period, she suffered a stroke and was diagnosed with patent foramen ovale (PFO). She has been referred for PFO closure.

Conclusions: A rare case is reported of familial Brugada syndrome with absence of the right coronary artery and patent foramen ovale, which may have combined to increase this patient's risk for ischemic stroke.

Keywords: Brugada Syndrome • Coronary Vessels • Defibrillators • Mutation

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/931535

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Background

Identified asymptomatic carriers of mutations related to Brugada syndrome are expected to increase in numbers with cascade screening, but no optimal management has been described based on specific genes. Even in manifest Brugada syndrome, as confirmed by type I ECG pattern, there is ongoing research with regard to risk scores that would better stratify patients [1-3]. On the other hand, a single coronary artery is a very rare congenital anomaly [4,5] and randomized controlled studies pertaining to its management are therefore difficult to design. It can be a potentially life-threatening condition and, so far, treatment has been based on symptoms and occurrence of an acute coronary syndrome [6]. We present a rare case of a 59-year-old woman with a family history of Brugada syndrome, who had the c.664C>T variant of the SCN5A gene, congenital absence of the right coronary artery, and patent foramen ovale. We also present our approach to her management.

Case Report

A 59-year-old female patient was referred to the Arrhythmia Clinic due to positive gene testing for Brugada syndrome, with a c.664C>T pathogenic variant mutation in the SCN5A gene. The testing was performed in the Manchester Centre for Genomic Medicine (Manchester, United Kingdom). She had a family history of Brugada syndrome, with one of her sons dying during his sleep at the age of 35 years, while the other son had an implantable cardioverter-defibrillator (ICD) implanted. She had no history of syncope or palpitations but she reported having anginal pain.

Previous medical history included type 2 diabetes mellitus controlled with metformin, hypertension treated with ramipril, bronchial asthma treated with beclometasone/formoterol inhaler, and she was an ex-smoker. In the past, she had been investigated for chest pain with an exercise treadmill test with no significant ST-T wave changes and myocardial perfusion scan which did not show any inducible ischemia, while the echocardiogram was normal.

Baseline electrocardiogram (ECG) showed sinus rhythm with nonspecific repolarization abnormalities in leads V1-V3 (**Figure 1**). ECG with precordial leads in higher intercostal spaces did not show features of a Brugada type I pattern either. The 24-h Holter monitor showed rare supraventricular and ventricular ectopics, but no ventricular arrhythmias, atrial tachyarrhythmias, or conduction abnormalities.

Given the typical chest pain, and while awaiting the results of the CTCA, the patient was started on aspirin, atorvastatin, and isosorbide mononitrate.

The computed tomography coronary angiogram (CTCA) showed congenital absence of the right coronary artery (RCA) with super-dominant left circumflex artery (LCx), with no stenoses and a calcium score of zero Agatston units (**Figure 2**).

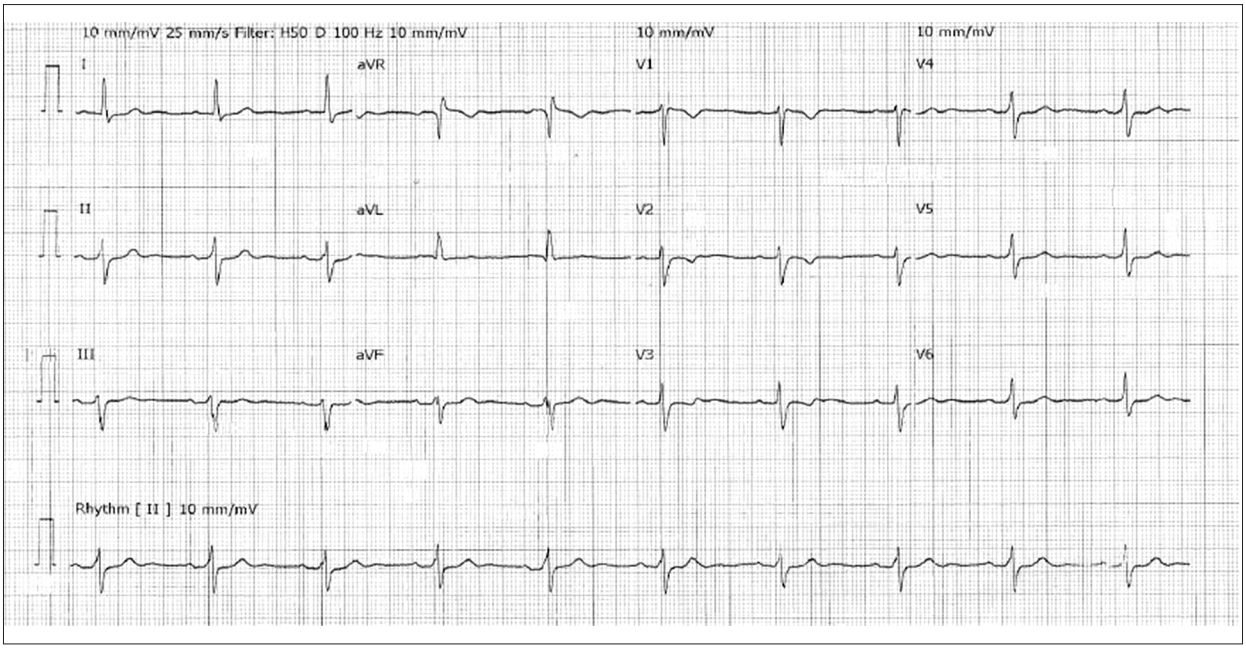

Figure 1. Baseline ECG. Baseline ECG shows sinus rhythm with nonspecific repolarization abnormalities in the form of T wave inversion in leads V1-V3 with no features suggestive of type 1 Brugada syndrome.

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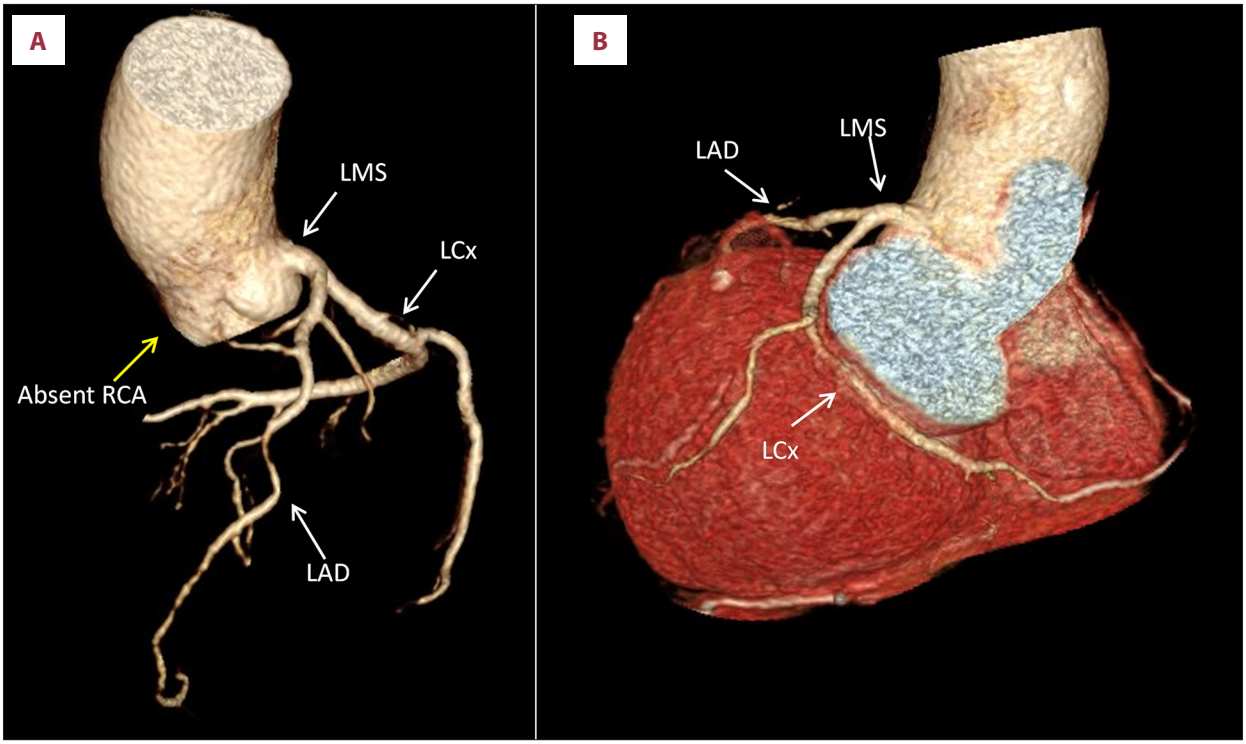

Figure 2. Computed tomography coronary angiogram. (**A**) Absence of take-off of the RCA from the right coronary sinus of Valsalva (yellow arrow) and normal origin of the LMS which bifurcates into the LAD and LCx (white arrows). (**B**) Course of the LCx on the posterior atrioventricular groove and continuation of its course in the RCA territory along with take-off of the posterior descending artery. LAD – left anterior descending artery; LCx – left circumflex artery; LMS – left main stem artery; RCA – right coronary artery.

Subsequently, the patient suffered an ischemic stroke, for which she was thrombolyzed with alteplase. Computed tomography of the brain showed an established wedge-shaped area of low density in the left temporoparietal region, in keeping with a recent infarct. Carotid artery Doppler evaluation showed mild plaque disease with stenoses of less than 30% in all carotid branches bilaterally. A bubble study was performed, which showed a small patent foramen ovale (PFO) with right-to-left shunt, only during Valsalva maneuver. The patient was referred for a work-up for the feasibility of percutaneous closure of the PFO.

The patient's case was discussed in our multidisciplinary team. It was decided not to proceed with ICD implantation as per current guidelines [7], but we discussed with the patient the option and clinical implications of an electrophysiology study with programmed ventricular stimulation (PVS) and implantable loop recorder. She declined any invasive procedure. Since the patient had tested positive for a mutation with a causative relationship with Brugada syndrome [8], we decided not to perform a drug provocation test with a sodium-channel blocking agent given that a positive test would not alter treatment in the absence of arrhythmic syncope/aborted sudden cardiac death. The patient decided to adopt a conservative approach with regular followup visits at our dedicated Arrhythmia Clinic. She was instructed to avoid sodium-channel blocking agents, excessive alcohol intake, and large meals. She was also advised to address fever promptly with antipyretics.

Regarding treatment for the congenital absence of the RCA, she remained under isosorbide mononitrate treatment, with symptom improvement. Aspirin and atorvastatin were discontinued and no intervention was planned, since the CTCA showed a calcium score of zero with no flow-limiting stenoses. SymptL1oms will be reviewed in 6-month intervals.

Discussion

This is a rare case of congenital absence of the right coronary artery in a patient with a Brugada-related gene mutation and PFO. Another case of Brugada syndrome with coexistence of PFO was previously reported by Versaci et al [9]. In their case, the Brugada phenotype was unmasked following administration of flecainide for atrial arrhythmias after PFO closure in the absence of any other congenital coronary artery anomaly.

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Our patient had tested positive for a gene variant known to cause Brugada syndrome and had a history of sudden cardiac death in the family along with a son who tested positive for the same mutation. We did not perform a full pedigree of the family, since according to local practice only first-degree relatives could be tested for the relevant mutation. The patient herself was asymptomatic from an arrhythmia point of view and little evidence exists regarding the management of asymptomatic carriers. The baseline ECG did not show typical features of Brugada syndrome [10]. SCN5A gene mutations have been correlated with inherited channelopathies such as Brugada syndrome and long-QT syndrome, but also with conduction disturbances, atrial arrhythmias, and contractile dysfunction resulting in dilated cardiomyopathy [11]. The 24 h tape from the Holter monitor did not show evidence of conduction disease and the echocardiogram was normal.

According to the current definition, only type I ECG morphology is diagnostic of Brugada syndrome, while type II and III ECG patterns do not support a diagnosis of Brugada syndrome. Furthermore, a provocation test with a Class I antiarrhythmic drug was not performed since, even if positive, it would not alter management according to current guidance, given the lack of syncope or documented ventricular tachycardia/fibrillation.

On the other hand, ICD implantation may be considered in patients with Brugada syndrome who develop ventricular fibrillation during programmed ventricular stimulation, but the level of evidence is low [7]. The option of an electrophysiology study was offered to the patient and, after discussion with her, we adopted a conservative approach with regular follow-up visits and recommendations regarding lifestyle measures.

A single coronary artery is a rare congenital anomaly of the coronary arteries, with an incidence among coronary angiographies of less than 0.1% [4,5]. The absence of the right coronary artery is a very rare variant with very few cases reported so far [6,12].

A classification was proposed by Lipton et al in 1979, based on the site of origin and the course of the single coronary artery [13]. This classification scheme was modified by Yamanaka and Hobbs in 1990 [14]. According to this classification, our patient had an L-I pattern, since the single artery originated from the left sinus of Valsalva, the super-dominant LCx continued its course in the RCA distribution area, and the posterior descending artery was a branch of the LCx.

Almost all studies reporting on the incidence of anomalies of the coronary arteries are based on retrospective analyses of invasive coronary angiographies. Nevertheless, it has been shown that CTCA can yield a prevalence of congenital coronary anomalies that is 4-fold higher when compared with invasive coronary angiography [15] and consequently it can obviate the need for invasive coronary angiography if no intervention is planned.

Guidelines regarding the management of this condition are difficult to establish, and treatment is guided by symptoms and the presence or absence of significant stenosis or occurrence of an acute coronary syndrome. In our patient, given a zero calcium score and the lack of significant stenosis, we opted for medical management with an anti-anginal agent and control of risk factors. Even though the myocardial perfusion scan was negative, the sensitivity of the test is not 100%, and in our patient the anginal symptoms could result from microvascular ischemia, given the history of diabetes, or slow flow in the area that would be supplied by the RCA (if existent). Given that no intervention would be appropriate in the absence of significant coronary artery stenosis in the CTCA, we decided not to offer an invasive coronary angiogram with or without a drug provocation test. On the other hand, another reason for the symptoms could be esophageal spasm, but this was less likely given the lack of any other accompanying symptoms related to the gastrointestinal tract.

The patient suffered a stroke, and it is unclear whether this was related to the SCN5A variant or the PFO. It is known that Brugada syndrome is related to atrial fibrillation [16] and has been correlated with an increased risk of stroke [17]. On the other hand, PFO is a known cause of stroke [18]. In our case, there was no documentation of atrial fibrillation in a 24 h Holter monitor tape and no history of palpitations, nor was there evidence of any other source of embolus found during the diagnostic work-up. Consequently, we concluded that the stroke was most likely related to the PFO and referred the patient for PFO closure, while we adopted an active monitoring strategy with repeated prolonged ECG monitors to detect any episodes of paroxysmal atrial fibrillation, since the patient declined an implantable loop recorder.

This is an interesting case of a patient with a combination of 2 conditions that can predispose a patient to stroke, and 2 conditions that can cause sudden cardiac death. This case highlights the fact that decisions are not always straightforward, and a stepwise approach, along with patient involvement, is needed to provide comprehensive individualized management.

Conclusions

A rare case of familial Brugada syndrome is reported, with absence of the right coronary artery and patent foramen ovale, which may have combined to increase this patient's risk for ischemic stroke.

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Conflict of Interest

None declared.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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