Risk stratification in families with history of idiopathic ventricular fibrillation

Mathieu Kruska, MD, Theano Papavassiliu, MD, Martin Borggrefe, MD, Stefan Baumann, MD, Anna Hohneck, MD, Boris Rudic, MD

From the First Department of Medicine-Cardiology, University Medical Centre Mannheim, Mannheim, Germany, and DZHK (German Centre for Cardiovascular Research), partner site Heidelberg/Mannheim, Mannheim, Germany.

Introduction

The examination of families with a high rate of sudden cardiac death (SCD) is reported to show a high diagnostic yield by identifying hereditary heart disease in 40% of the families.[1] A thorough examination of patients who survived idiopathic ventricular fibrillation (IVF) or sudden cardiac arrest without an apparent cause is vital for appropriate prophylaxis and treatment among relatives. We present a case of a patient with a family history of SCD and IVF, underlining the importance of obtaining the diagnosis of families with IVF and SCD.

Case report

A 34-year-old male patient was admitted to our hospital owing to having survived cardiac arrest caused by ventricular fibrillation (VF). The patient had been carefully examined 18 years ago because of a family history of sudden death (Figure 1). The patient's father had survived VF without evidence of underlying heart disease. The father then received an implantable cardioverter-defibrillator for the secondary prevention of IVF. In 2001, the father died at the age of 46 years owing to an electrical storm. Unfortunately, at that time an autopsy was not performed. At least 4 other, predominantly male family members between the ages of 18 and 50 years have died suddenly in unexplained circumstances.

Taking the family history and the father's death into account, the patient underwent a thorough diagnostic work-up at the age of 16. No coronary anomalies were found. A ventriculography of the right ventricle (RV) and an electrophysiological study including programmed ventricular stimulation were completely normal. Echocardiography showed no evidence of structural heart disease, with normal right and left ventricular function. An intravenous ajmaline challenge was not suggestive of Brugada syndrome. Notably, a resting electrocardiogram (ECG) revealed T-wave inversions in inferior leads and leads V_4–V_6. Aside from a premature ventricular complex (PVC) burden of 500 per day, serial Holter ECGs revealed no tachyarrhythmias during follow-up. Furthermore, a cardiac magnetic resonance (CMR) of the heart had been performed on the patient in 2006 in which no pathologic findings were observed. A hypertrophy of the moderator band and prominent trabeculation of the RV were seen as normal owing to the young age of the patient. No late gadolinium enhancement was evident, whereas the right and left ventricular function remained normal, as were the dimensions of the heart chambers. The patient did not report any syncope or any further symptoms.

In 2019, the patient was suffering from an out-of-hospital cardiac arrest owing to VF. In contrast to the previous examination when the patient was 16, echocardiography revealed a dilated RV and regional dyskinesia. Compared to prior resting ECGs, novel epsilon waves and T-wave inversions were present in V_1–V_3 (Figure 2). A newly revealed

KEY TEACHING POINTS

- A thorough examination of patients who survived idiopathic fibrillation or sudden cardiac arrest without apparent cause is vital for appropriate prophylaxis and treatment among the patients' relatives.
- The cause of idiopathic ventricular fibrillation or familial sudden cardiac death might be a progressive underlying heart disease.
- The close follow-up of patients with idiopathic ventricular arrhythmias and their unaffected family members is a necessity.

KEYWORDS Arrhythmogenic right ventricular cardiomyopathy; Hereditary heart disease; Idiopathic ventricular fibrillation; Risk stratification; Sudden cardiac death

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Address reprint requests and correspondence: Dr Boris Rudic, First Department of Medicine, Faculty of Medicine Mannheim, University Medical Centre Mannheim (UMM), University of Heidelberg, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany. E-mail address: boris.rudic@umm.de.

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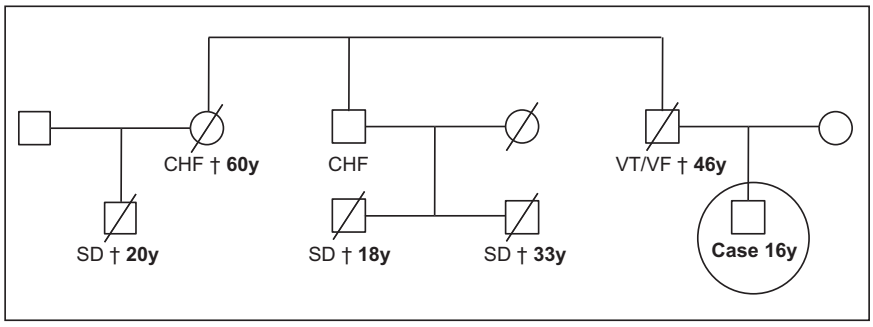

Figure 1 Family history. CHF = chronic heart failure; SD = sudden death; VF = ventricular fibrillation; VT = ventricular tachycardia.

incomplete right bundle branch block is common in arrhythmogenic right ventricular cardiomyopathy (ARVC), indicating right ventricular activation delay.[2] In addition, the current ECG showed left axis deviation and a new left anterior hemiblock. A CMR confirmed the diagnosis of ARVC with reduced ejection fraction of the RV, bulging of the basal RV free wall, and late gadolinium enhancement of the RV wall. There was no evidence of left ventricular involvement. These CMR and ECG findings were in line with the modified task force criteria for the diagnosis of ARVC.[3] Molecular genetic analysis did not identify pathogenic variants associated with ARVC. An implantable cardioverter-defibrillator was implanted in the patient, optimal medical heart failure therapy was initiated, and the patient was released from the hospital. The follow-up remained uneventful.

Discussion

In this report, it is noteworthy that no strong clinical evidence of the presence of ARVC was found, either at the initial diagnostic work-up when the patient was 16 or during the long-term follow-up in 2006. T-wave inversions in the inferior leads and in leads V_4–V_6 were initially the only relevant finding in our patient, suggesting left ventricular involvement of an ARVC as well as the left axis deviation and left anterior fascicular block.[2,4] However, no evidence of left ventricular involvement was found in the CMR examination. After the patient's out-of-hospital cardiac arrest in 2019, an epsilon wave and anteroseptal T-wave inversions in V_1–V_3 were observed, the hallmark sign of ARVC, normally related to the presence of right ventricular dilatation.[5,6]

A common clinical presentation of ARVC is palpitations or syncopes because of a high PVC burden or monomorphic ventricular tachycardia, typically becoming clinically apparent between the second and fourth decade of life.[3] However, clinical presentation of ARVC appeared rather unlikely in this case report. Furthermore, initially, T-wave inversions did not occur in the right precordial leads, which are present in up to 87% of patients with ARVC.[6] Additionally, with advanced disease progression, neither an increase of the PVC burden nor spontaneous ventricular tachyarrhythmias could be detected. Despite the preceding diagnostic examination, the patient's having survived SCD was the first clinical manifestation of the disease in this patient.

In the first CMR in 2006, no changes of tissue composition or dynamic morphology were seen in the patient. However, as mentioned, a prominent trabeculation and hypertrophy of the moderator band of the RV were observed but seen as normal for the age of the patient at the time. These same conditions have been noted in patients with ARVC, but these findings lack specificity and therefore are not part of the modified task force criteria for the diagnosis of ARVC.[7,8] However, technical advances and new imaging biomarkers may provide incremental value in the diagnosis of early stages of the disease. Feature-tracking CMR imaging has revealed reduced regional strain of the RV in ARVC.[9] Accordingly, feature-tracking CMR may be a decisive element in detecting an early disease stage and in the risk stratification. Other approaches such as electroanatomical mapping allow the identification of otherwise unrecognized myocardial structural abnormalities in patients with idiopathic ventricular arrhythmias and may also contribute to the early diagnosis of ARVC.[10]

For the presented patient, the untimely deaths of his male relatives and the supposed IVF of his father are suggestive of hereditary cardiac diseases such as ARVC. Male predominance in ARVC is explained by a more severe disease phenotype in the male sex and seems to fit the family described.[11] The male sex is associated with a higher risk of ventricular arrhythmias.[12]

The patient's family history of SCD and IVF already indicates the high risk of the patient. Although the definition of IVF has changed during the years, the essential issue is the absence of a substrate for VF and exclusion of specific diseases.[13,14] In the ESC guidelines, IVF is defined as the absence of a discernible structural or genetic heart disease, which may change in the future owing to better diagnostics.[15] Available data from researchers investigating patients and their relatives with SCD or IVF are a result of the use of different diagnostic algorithms. Therefore, the proportion of patients with an underlying but undetected disease is elusive in these cohorts. However, in a recent French study, it was found that in about half of the patients with unexplained sudden cardiac arrest owing to IVF, the triggering cause for the occurrence of VF could be identified with comprehensive diagnostics. The evaluation of families with a high frequency of SCD shows high

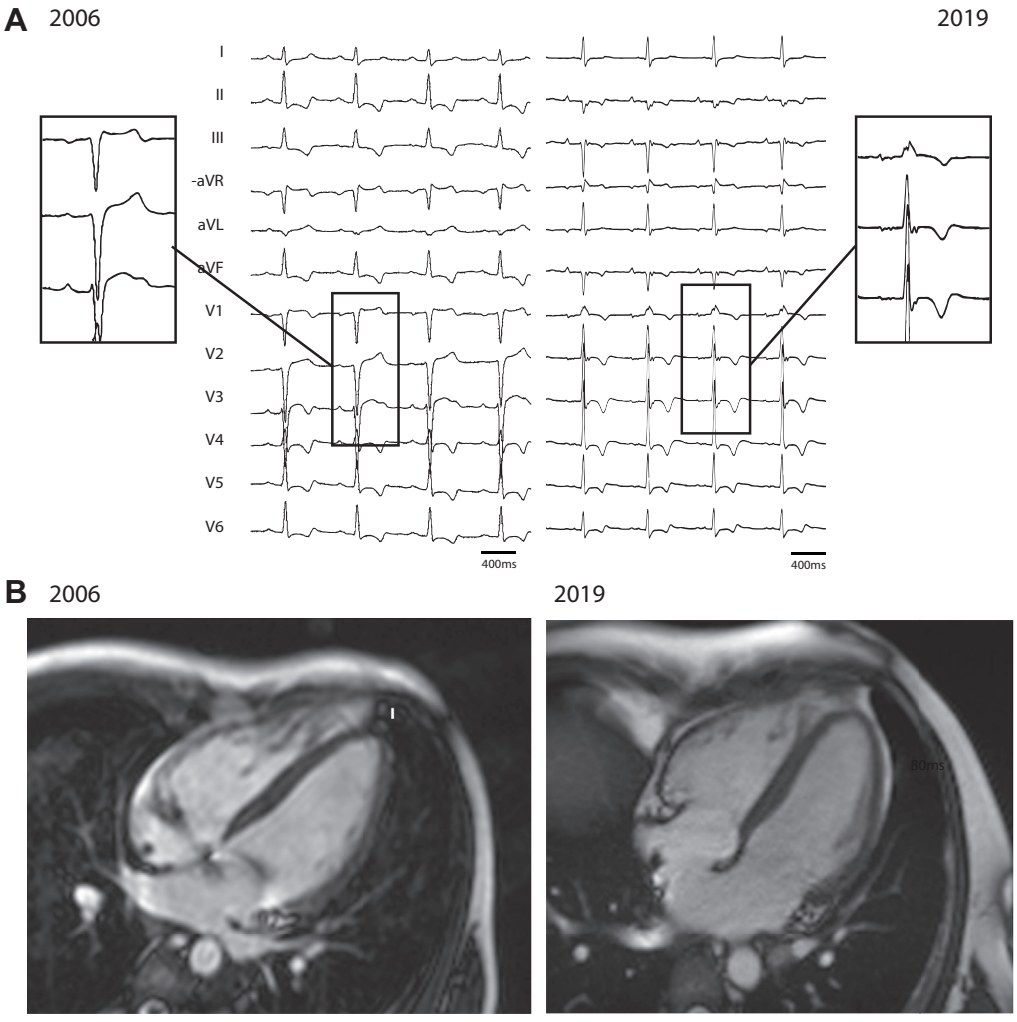

Figure 2 Resting electrocardiogram (**A**) and cardiac magnetic resonance (**B**) at follow-ups in 2006 and in 2019.

diagnostic yield by identifying the underlying heart disease in 40% of families.[16]

Conclusion

Hereditary heart diseases differ not only in penetrance but also in the timeframe of change from a concealed to an overt phenotype. The cause of IVF or familial SCD could be such a progressive underlying heart disease. The resulting risk stratification should be considered in these patients and their relatives, allowing early diagnosis and implementation of primary prevention measures before the potential occurrence of life-threatening events as a first presentation. This case report emphasizes close follow-up of patients with idiopathic ventricular arrhythmias and their unaffected family members to identify a potentially underlying concealed disease.

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References

1. Tan HL, Hofman N, van Langen IM, van der Wal AC, Wilde AA. Sudden unexplained death: heritability and diagnostic yield of cardiological and genetic examination in surviving relatives. Circulation 2005;112:207–213.
2. Jain R, Dalal D, Daly A, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia. Circulation 2009;120:477–487.
3. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. Eur Heart J 2010;31:806–814.
4. Steriotis AK, Bauce B, Daliento L, et al. Electrocardiographic pattern in arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol 2009; 103:1302–1308.
5. Nava A, Canciani B, Buja G, et al. Electrovectorcardiographic study of negative T waves on precordial leads in arrhythmogenic right ventricular dysplasia: relationship with right ventricular volumes. J Electrocardiol 1988;21:239–245.
6. Marcus FI. Prevalence of T-wave inversion beyond V1 in young normal individuals and usefulness for the diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. Am J Cardiol 2005;95:1070–1071.
7. Tandri H, Calkins H, Nasir K, et al. Magnetic resonance imaging findings in patients meeting task force criteria for arrhythmogenic right ventricular dysplasia. J Cardiovasc Electrophysiol 2003;14:476–482.
8. Molinari G, Sardanelli F, Gaita F, et al. Right ventricular dysplasia as a generalized cardiomyopathy? Findings on magnetic resonance imaging. Eur Heart J 1995;16:1619–1624.
9. Bourfiss M, Vigneault DM, Aliyari Ghasebeh M, et al. Feature tracking CMR reveals abnormal strain in preclinical arrhythmogenic right ventricular dysplasia/cardiomyopathy: a multisoftware feasibility and clinical implementation study. J Cardiovasc Magn Reson 2017;19:66.

10. Castro SA, Pathak RK, Muser D, et al. Incremental value of electroanatomical mapping for the diagnosis of arrhythmogenic right ventricular cardiomyopathy in a patient with sustained ventricular tachycardia. HeartRhythm Case Rep 2016;2:469–472.
11. Rigato I, Bauce B, Rampazzo A, et al. Compound and digenic heterozygosity predicts lifetime arrhythmic outcome and sudden cardiac death in desmosomal gene-related arrhythmogenic right ventricular cardiomyopathy. Circ Cardiovasc Genet 2013;6:533–542.
12. Bosman LP, Sammani A, James CA, et al. Predicting arrhythmic risk in arrhythmogenic right ventricular cardiomyopathy: a systematic review and meta-analysis. Heart Rhythm 2018;15:1097–1107.
13. Survivors of out-of-hospital cardiac arrest with apparently normal heart. Need for definition and standardized clinical evaluation. Consensus Statement of the Joint Steering Committees of the Unexplained Cardiac Arrest Registry of Europe and of the Idiopathic Ventricular Fibrillation Registry of the United States. Circulation 1997;95:265–272.
14. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 2013;10:1932–1963.
15. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Europace 2015; 17:1601–1687.
16. Waldmann V, Bougouin W, Karam N, et al. Characteristics and clinical assessment of unexplained sudden cardiac arrest in the real-world setting: focus on idiopathic ventricular fibrillation. Eur Heart J 2018;39:1981–1987.