Arrhythmogenic right ventricular cardiomyopathy (ARVC) is rarely diagnosed in childhood. We describe the case of a 9-year-old girl with genetically confirmed ARVC who presented with syncope, ventricular arrhythmia, and biventricular myocardial dysfunction. This case highlights the need for development of pediatric ARVC diagnosis criteria specific for pediatric patients and discusses potential diagnostic improvement using echocardiographic deformation imaging.

**ABSTRACT**

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is rarely diagnosed in childhood. We describe the case of a 9-year-old girl with genetically confirmed ARVC who presented with syncope, ventricular arrhythmia, and biventricular myocardial dysfunction. This case highlights the need for development of pediatric ARVC diagnosis criteria specific for pediatric patients and discusses potential diagnostic improvement using echocardiographic deformation imaging.

**PRESENTATION**

A 9-year-old girl was admitted to the authors’ hospital for evaluation of recurrent syncope. She was not taking any medication. Physical examination was unremarkable.

**MEDICAL HISTORY**

Prior to presentation, she experienced daily episodes of palpitations with nearly syncope and 2 episodes of syncope during exercise (i.e., gymnastics class at school). She did not have chest pain or dyspnea. Her family history was negative for sudden cardiac death or cardiomyopathy. She did not participate in

**LEARNING OBJECTIVES**

- Since the diagnostic Task Force Criteria were derived in a predominantly adult cohort, their use in children should be considered experimental, and physicians should be aware of their limitations in the pediatric population.
- Echocardiographic deformation imaging is useful for diagnostic evaluation of arrhythmogenic right ventricular cardiomyopathy.
- Given the incomplete penetrance of disease, genetic testing should be integrated in the evaluation of young patients with unexplained cardiomyopathy, even without a family history of heart disease.
**DIFFERENTIAL DIAGNOSIS**

Syncope in children has a broad differential (Table 1). Exercise-induced syncope associated with palpitations is highly suspicious of a cardiac cause, especially ventricular arrhythmia.

### INVESTIGATIONS

**ELECTROCARDIOGRAPHY.** The 12-lead electrocardiography (ECG) showed sinus rhythm, right heart axis, normal conduction intervals, high R-wave amplitude, T-wave inversions in leads V₁ to V₄ and flattened T waves in the inferior leads (Figure 1). Twenty-four-hour Holter monitor revealed 1,689 premature ventricular complexes and 4 episodes of nonsustained ventricular tachycardia with unknown morphology at 250 to 270 beats/min.

**ECHOCARDIOGRAPHY.** Two-dimensional trans-thoracic echocardiography showed a morphologically normal heart and left ventricular (LV) wall thickness (Video 1). Mild biventricular dilation and systolic dysfunction were present (LV ejection fraction [EF] of 50% and tricuspid annular plane systolic excursion of 17 mm). Task Force Criteria (TFC) for ARVC were not met.

### TABLE 1 Differential Diagnosis of Syncope

| Differential Diagnosis                          | Arguments Pro and Con Diagnosis |
|------------------------------------------------|--------------------------------|
| Cardiac causes                                  |                                |
| Long QT syndrome                               | Normal QT interval and presence of significant structural heart disease makes diagnosis unlikely. |
| RVOT/IVOT tachycardia                          | Presence of significant structural heart disease makes diagnosis unlikely. |
| Catecholaminergic polymorphic ventricular tachycardia | Patients with CPVT present with exercise-induced ventricular arrhythmias in absence of structural heart disease. In this case, presence of significant structural heart disease in this case makes CPVT diagnosis unlikely. |
| NB patients in the "concealed" phase of ARVC can present with exercise-induced ventricular arrhythmias in absence of structural disease, a presentation that mimics CPVT. However, CPVT does not progress into structural heart disease, has a different genetic etiology and ventricular arrhythmias have a polymorphic character compared to monomorphic left bundle branch block morphology in cases of classical ARVC. |
| Cardiomyopathy                                  |                                |
| Dilated cardiomyopathy                         | Mild LV dilation (104 mL/m²) and LV dysfunction (49%) are suggestive of diagnosis. The incidence of DCM in children is far higher compared to ARVC which is more commonly seen during young adulthood. However, DCM was not the most likely diagnosis because the evident LV involvement and the occurrence of ventricular arrhythmias in the early stages of disease are more suggestive of ARVC with LV involvement. Patients with ARVC and LV involvement can mimic patients with DCM, however the arrhythmic risk and genetic etiology are different. |
| Hypertrophic (obstructive) cardiomyopathy       | Not likely, LV myocardial segment diameters are within two standard deviations when corrected for age. |
| Arrhythmogenic right ventricular cardiomyopathy | Most likely diagnosis, due to presentation with ventricular tachycardia, significant PVC burden, focal akinesia of the RV with epicardial LGE with RV dilation and dysfunction. Diagnosis confirmed by pathogenic desmosomal variants. |
| Myocardial Inflammation                         |                                |
| Sarcoïdosis                                     | No evidence of systemic or cardiac sarcoidosis (Table 2). |
| Myocarditis                                     | No evidence of active myocarditis on T2 imaging of CMR and normal troponin levels. Normal inflammatory markers, virus serology, and bacterial cultures (Table 2). |
| Other cardiac causes                            |                                |
| Valvular disease                                | Echocardiography showed no severe valvular disease. |
| Acute myocardial infarction or ischemia         | No acute coronary syndrome and no signs of an aberrant coronary artery on imaging. |
| Acute aortic dissection                         | No evidence of aortic dissection on echocardiography or CMR. |
| Cardiac masses                                  | No myxoma or cardiac tumor on echocardiography or CMR. |
| Cardiac tamponade                               | No pericardial effusion on echocardiography or CMR or signs. |
| Pulmonary hypertension                          | Other than RV dilation, no other signs of pulmonary hypertension on echocardiography or CMR. |
| Pulmonary embolism                              | Besides RV dilation, no other signs of pulmonary embolism echocardiography or CMR. |
| Neurally mediated (reflex) syncope               |                                |
| Situational                                     | Clear cardiac pathology and relation with exercise make cardiac cause more likely. |
| Vasovagal                                       | Clear cardiac pathology and relation with exercise make cardiac cause more likely. |
| Micturition                                     | Syncope episodes had no relation with micturition. |
| Carotid sinus syndrome/hypersensitivity         | Clear cardiac pathology makes cardiac cause more likely. |

ARVC = arrhythmogenic right ventricular cardiomyopathy; CMR = cardiac magnetic resonance imaging; CPVT = catecholaminergic polymorphic ventricular tachycardia; DCM = dilated cardiomyopathy; HCM = hypertrophic (obstructive) cardiomyopathy; LGE = late gadolinium enhancement; LV = left ventricle; LVOT = left ventricular outflow tract; NB = nota bene; PVC = premature ventricular complex; RV = right ventricle; RVOT = right ventricular outflow tract; VT = ventricular tachycardia.
fulfilled as no right ventricular (RV) wall motion abnormalities were present. However, deformation imaging using speckle tracking indicated biventricular dysfunction (Figures 2 and 3). RV subtricuspid strain showed systolic pre-stretch, as may be observed in adult ARVC (1). Global longitudinal strain was significantly reduced in both the LV (−13.5%; normal: >−18.5%) and RV (−20.0%; normal: >−26.5%).

**CARDIAC MAGNETIC RESONANCE IMAGING.** Cardiac magnetic resonance (CMR) confirmed biventricular dilation and dysfunction (LV indexed end-diastolic volume [EDV]: 104 ml/m² and LVEF of 49%; RV EDV: 117 ml/m²; and RVEF: 36%) (Figure 1, Video 2). Akinesia was observed in the inferior RV and RV outflow tract which resulted in a major criterion for ARVC. T2-weighted images showed no myocardial edema suggestive of myocarditis. Epicardial patchy late gadolinium enhancement was present in the LV, midwall septum, extending to the inferior RV.

**MISCELLANEOUS.** Laboratory examinations, chest radiography, and ophthalmological examination (Tables 1 and 2) did not yield a specific diagnosis.

**DIAGNOSTIC CONFIRMATION BY GENETIC TESTING.** ARVC with LV involvement was thought to be more likely than dilated cardiomyopathy (DCM) due to the evident RV involvement and occurrence of episodes of ventricular arrhythmia in the early stages of the disease (Table 1). However, ARVC could not be definitively diagnosed during clinical evaluation because the 2010 TFC for ARVC were not fulfilled (Table 3) (2).
Genetic testing confirmed the diagnosis of ARVC. The patient was heterozygous for 2 plakophilin (PKP2) variants, c.397C>T, p.(Gln133∗), classified as pathogenic, and c.2615C>T, p.(Thr872Ile), classified as variants of unknown significance; and 1 pathogenic desmoglein (DSG2) variant (c.1003A>G, p.(Thr335Ala)). Cascade screening confirmed ARVC diagnosis in her asymptomatic mother (age 44 years) who carried both PKP2 variants and had T-wave inversions in V1 to V3, and a major CMR criterion. The mother of the patient was treated with sotalol and received a primary prophylactic implantable cardioverter-defibrillator (ICD). The girl’s asymptomatic father (age 50 years) carried the DSG2 variant and had normal cardiac evaluation (including an ECG, an echocardiogram, and CMR).

**MANAGEMENT**

The patient was started on sotalol therapy to suppress her symptomatic ventricular arrhythmia episodes and spironolactone to prevent further adverse ventricular remodeling. She was advised to avoid competitive sports. A subcutaneous ICD was implanted before she was discharged.

**DISCUSSION**

ARVC is rarely diagnosed before adolescence, and the diagnostic TFC are not validated for use in pediatric
cohorts (4,5). The case presented here emphasizes the limitations of the TFC in children and highlights opportunities for improvement.

LOW SENSITIVITY OF THE TFC IN PEDIATRIC PATIENTS. The diagnostic TFC were developed in a predominantly adult cohort (2). To deal with this limitation, repolarization abnormalities were excluded from the TFC in children <14 years of age. Of note, CMR cutoff values were based on a comparison between adult ARVC probands and controls, the implications of which for pediatric ARVC evaluation remains unknown (2,6). The present case illustrates the fact that the TFC are relatively insensitive for pediatric diagnosis, and future studies should focus on validation in pediatric cohorts and development of imaging criteria specific for children (3).

LOW SENSITIVITY OF IMAGING CRITERIA IN EARLY ARVC. In this patient, both echocardiography and CMR were suggestive of ARVC, but only CMR provided a major criterion for ARVC diagnosis. This is not unexpected, as echocardiography is less sensitive for ARVC evaluation than CMR (7). However, this case illustrates the fact that echocardiographic deformation imaging may unmask the abnormal structural substrate, suggesting a possible role in screening for ARVC.

BIVENTRICULAR INVOLVEMENT IN ARVC. Left ventricular involvement is well recognized in ARVC and leads to diagnostic overlap with DCM. Indeed, this patient clearly had biventricular involvement and, hence, should be regarded as spanning the spectrum between ARVC and DCM. Given the overlapping phenotypes, it seems important to be vigilant for arrhythmic risk and genetic causes in apparent DCM cases.

GENOTYPE-PHENOTYPE CORRELATION. Early development of ARVC in this pediatric case might have been influenced by variants in both the PKP2 and the DSG2 genes. Indeed, multiple pathogenic variants are associated with worse prognosis (8). In contrast, although exercise is a known environmental modifier of the ARVC phenotype, this patient did not participate in vigorous physical exercise.

FOLLOW-UP. During 2.5 years of follow-up, the patient did not experience syncope or ICD interventions, and the LVEF and RVEF were stable. Device interrogation revealed frequent episodes of nonsustained ventricular tachycardia (maximum: 160 beats/min) without requiring device therapy and a stable premature ventricular complex burden of 5% of QRS complexes.

CONCLUSIONS

This report provides detailed phenotypic information for a young girl carrying 2 pathogenic desmosomal variants. Albeit a diagnosis of ARVC is highly
likely to explain her symptoms, the data highlight the fact that the diagnostic TFC have low sensitivity for disease among children. Echocardiographic deformation imaging may have added value for ARVC screening.

### REFERENCES

1. Mast TP, Teske AJ, Walmsley J, et al. Right ventricular imaging and computer simulation for electromechanical substrate characterization in arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol 2016;68:2185–97.

2. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation 2010;121:1533–41.

3. Towbin JA, McKenna WJ, Abrams DJ, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. Heart Rhythm 2019;16:e373–407.

4. DeWitt ES, Chandler SF, Hylind RJ, et al. Phenotypic manifestations of arrhythmogenic cardiomyopathy in children and adolescents. J Am Coll Cardiol 2019;74:346–58.

5. Te Riele A, James CA, Sawant AC, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy in the pediatric population: clinical characterization and comparison with adult-onset disease. J Am Coll Cardiol EP 2015;1:551–60.

6. Maceira AM, Prasad SK, Khan M, Pennell DJ. Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. Eur Heart J 2006;27:2879–88.

7. Roudijk R, et al. JACC: CASE REPORTS, VOL. 2, NO. 6, 2020. Pediatric ARVC: A Rare Cause of Syncope. JUNE 2020:919–24.

8. Levy PT, Sanchez Mejia AA, Machefsky A, Fowler S, Holland MR, Singh GK. Normal ranges of right ventricular systolic and diastolic strain measures in children: a systematic review and meta-analysis. J Am Soc Echocardiogr 2014;27:625–36.

9. Marcus KA, Mavinkurve-Groothuis AM, Barends M, et al. Reference values for myocardial two-dimensional strain echocardiography in a healthy pediatric and young adult cohort. J Am Soc Echocardiogr 2011;24:625–36.

10. Levy PT, Sanchez Mejia AA, Machefsky A, Fowler S, Holland MR, Singh GK. Normal ranges of right ventricular systolic and diastolic strain measures in children: a systematic review and meta-analysis. J Am Soc Echocardiogr 2014;27:625–36.

**ADDRESS FOR CORRESPONDENCE:** Dr. Anneline S.J.M. te Riele, University Medical Center Utrecht, Heidelberglaan 100, 3508 GA, Utrecht, the Netherlands. E-mail: ariele3@umcutrecht.nl.

**KEY WORDS** arrhythmogenic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, deformation imaging, desmosomal mutations, genetic screening, pediatrics, ventricular tachycardia

### APPENDIX

For supplemental videos, please see the online version of this paper.