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CASE SERIES

Arrhythmogenic Cardiomyopathy in Children. Case Series and Review of the Literature

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ABSTRACT

Arrhythmogenic cardiomyopathies (ACM) are rare inherited cardiac disorders, with an incidence below 1% in adults and an undetermined prevalence in pediatric populations. Formerly recognized primarily as arrhythmogenic right ventricular cardiomyopathy (ARVC), affecting exclusively the right ventricle (RV), recent diagnostic advancements have shed light on the involvement of the myocardium in ACM, revealing fibrous infiltration in both ventricles. In 2023, the European Society of Cardiology introduced updated phenotypic classifications of cardiomyopathy, highlighting the coexistence of multiple types within families and the potential transition from one cardiomyopathy to another. We present a case series comprising four pediatric cases of ARVC with diverse presentations and outcomes. Subsequent evaluations unveiled both left ventricle (LV) and RV dysfunction, culminating in a diagnosis of ARVC based on the 2020 diagnostic criteria. Additionally, genetic testing uncovered mutations in genes associated with cardiomyopathies. Cardiac magnetic resonance imaging (MRI) corroborated the biventricular involvement, aligning with a diagnosis of ACM per the 2020 Padua criteria. In conclusion, recent updates in diagnostic criteria have refined the classification of ACM, underscoring the importance of cardiac MRI and morphological features for precise diagnosis. Genetic testing has identified novel mutations linked to cardiomyopathy, emphasizing the significance of personalized treatment strategies and genetic counselling for affected individuals and their families.

Keywords: arrhythmogenic cardiomyopathies, pediatric heart failure, pediatric cardiomyopathies, inherited disease, genetic testing

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INTRODUCTION

Arrhythmogenic cardiomyopathies (ACM) are rare inherited cardiomyopathies, with an incidence of 0.078% in adults.[1] However, the prevalence in pediatric patients remains unknown owing to limited studies focusing on this population. This lack of data raises concerns about a potential underdiagnosis of ACM in children.

In the past, arrhythmogenic right ventricle (RV) dysplasia with fibro-fatty infiltration of the RV was considered cardiomyopathy affecting only the RV. However, recent technological advancements revealed that fibrous infiltration of the myocardium can occur in both ventricles. In 2023, the Task Force of the European Society of Cardiology described the new phenotypic types of cardiomyopathies and emphasized that different types of cardiomyopathies

TABLE 2. Correlation analysis of patient characteristics and cystatin C levels

	Case 1	Case 2	Case 3	Case 4
Age at diagnosis	1.4 years	12 years	12 years	17 years
Symptoms	• Intolerance to physical exertion • Palpitations • Dizziness • Precordial pain	• Intolerance to physical exertion • Palpitations • Diaphoresis	• Cardiac arrest	• Intolerance to physical exertion • Weakness • Extreme fatigue
Family history	–	• Father and sister DCM and SCD • Brother DCM	• Uncle WPW syndrome • Uncle HCM • Uncle PVC with LBBB morphology	• Grandfather SCD
ECG	• Negative T waves in V1–V4	• Negative T waves in V1–V4	• Negative T waves in V2–V5 • Diffuse concave ST-segment elevation • PVC with LBBB morphology	• Negative T waves in V1–V3 • RBBB • Left anterior fascicular hemiblock
Holter ECG	• Multifocal PVCs with LBBB morphology	• Multifocal PVCs with RBBB and LBBB morphology • Non-sustained VT	• Multifocal PVCs with RBBB and LBBB morphology	• Multifocal PVCs with RBBB and LBBB morphology • Non-sustained VT
Echocardiography	• Mildly dilated LV, initial LVEF 50%, then 60–65% • Mild mitral insufficiency	• Mildly dilated LV, LVEF 50% • Minor mitral insufficiency	• RV hypokinesia and dyskinesia of RV free wall, RV apical aneurysm	• Severely dilated LV, LVEF 15% • Thrombosis of the walls and apex of both ventricles
MRI	• LVEF 57%, segmental hypokinesia • RVEF 46.5%, increased indexed volume (118 ml/m2), dilatation of the anterior portion of the RV free wall	• LVEF 52%, mild inferior and inferoseptal hypokinesia • RVEF 43%, increased indexed volume (93.8 ml/m2), regional dyskinesia of the RV free wall	• LVEF 60.5%, with depressed global longitudinal strain (-14.6) • RVEF 41%	• LVEF 27%, global hypokinesia • Subendocardial fibrotic lesions • RVEF 51%, increased indexed volume (221 ml/m2) with accentuated trabeculae
Genetics	Mutation in the TTN gene (VUS)	Mutation in the TTN gene (VUS)	Mutation in the FLNC gene (VUS)	Mutation in the DSC2 gene (VUS)
Treatment	Pharmacological	ICD implantation	ICD implantation	ICD implantation

DCM, dilated cardiomyopathy; DSC2, Desmocollin 2 gene; EF, ejection fraction; FLNC, Filamin-C gene; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LV, left ventricle; PVC, premature ventricular complexes; RV, right ventricle; SCD, sudden cardiac death; TTN, titin gene; VT, ventricular tachycardia; VUS, variant of uncertain significance; WPW, Wolf–Parkinson–White syndrome

can coexist in the same family, and that one type of cardiomyopathy can potentially evolve into another.[1]

This study aims to present four distinct cases of ACM in pediatric patients (Table 1) to provide valuable insights into the clinical manifestations, diagnostic challenges, management strategies, and outcomes associated with ACM in the pediatric population. We seek to emphasize the importance of early recognition, accurate diagnosis, and individualized management approaches in optimizing outcomes for pediatric patients.

CASE 1

We present the case of a 17-year-old female patient diagnosed at the age of 1.4 years with dilated cardiomyopathy (DCM) based on the echocardiography exam, possibly post-myocarditis owing to recurrent respiratory infections and absent family history. At the moment of diagnosis, because of limited resources and the patient's age, we were unable to conduct an MRI exam. Over the years, the patient exhibited symptoms such as intolerance to physical exertion, palpitations, dizziness, and precordial pain. Echocardiograms showed mild DCM with an initial LV ejection fraction (EF) of 50% that stabilized at 60–65% over the years, and mild mitral insufficiency. Repeated electrocardiograms (ECG) revealed negative T waves in V1–V4. After 2 years of follow-up, Holter ECG revealed polymorphic premature ventricular contractions (PVC). Despite the small number of PVCs with left bundle branch block (LBBB) morphology (>500/day, below 1% of the whole record), the patient was symptomatic. It is important to mention that in 2020, the patient was diagnosed with polymyositis.

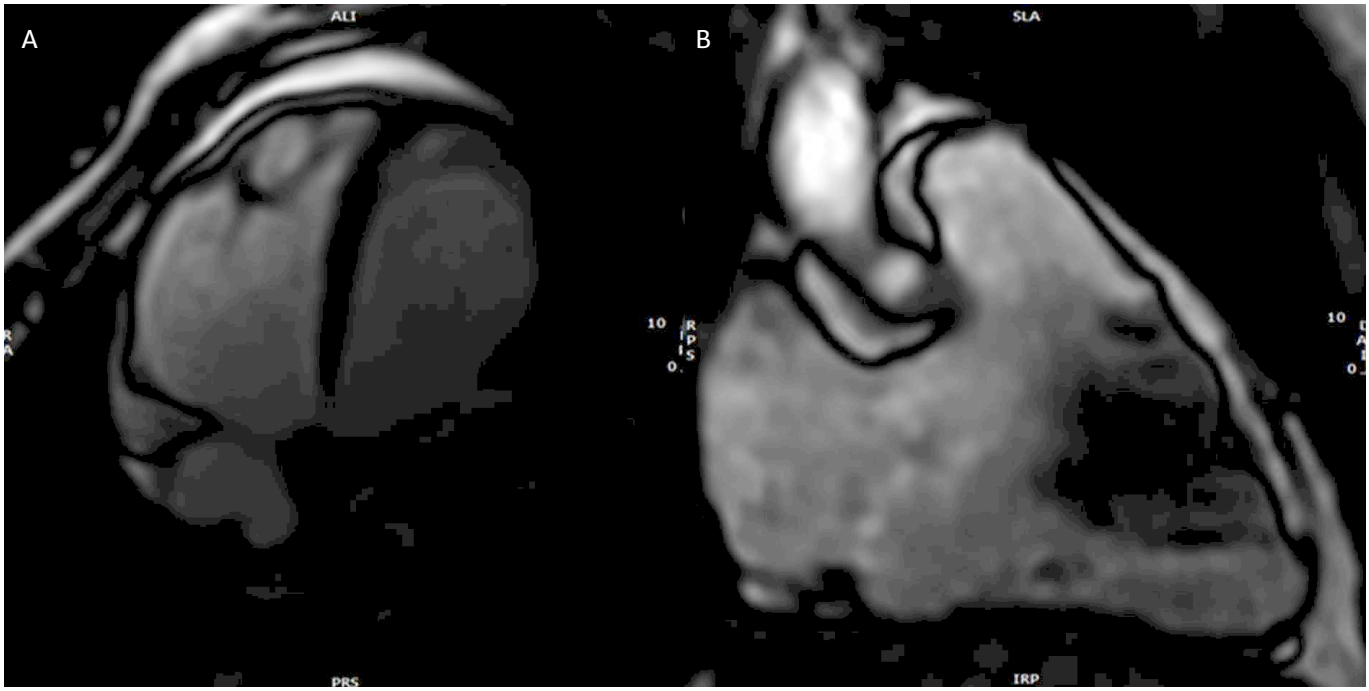

FIGURE 1. MRI scans from our cases. **A.** Apical 4-chamber view of cardiac MRI scan of the first patient reveals biventricular dilatation. **B.** Right ventricular vertical long-axis view scan in our second patient shows dilated right ventricle, with elevated indexed volume.

An MRI scan performed when the patient was 16 years old revealed an LVEF of 57%, with segmental hypokinesia in the mid-inferior and inferolateral walls. Conversely, the RV showed an increased indexed volume with a depressed systolic function (Figure 1A). Additionally, the MRI found the presence of several diverticular dilations along the anterior portion of the RV free wall. No signs of edema or diffuse myocardial fibrosis were detected. According to the 2020 ARVC diagnostic criteria,[2] an ACM diagnosis was made. Genetic testing revealed a mutation in the TTN gene in a variant of uncertain significance (VUS). In this particular case, ICD implantation was not considered, as there were only a few PVCs without VT episodes; hence, continuous monitoring and pharmacological treatment was chosen.

CASE 2

A 14-year-old female patient with a positive family history (father and a sister diagnosed with DCM with premature sudden cardiac death (SCD) and a brother diagnosed with DCM) was admitted to our clinic with complaints of exercise intolerance, diaphoresis, and palpitations. Transthoracic echocardiography revealed mild DCM with an LVEF of 50% and minor mitral regurgitation. The ECG revealed a prolonged QTc interval (500–550 ms) and negative T waves in V1–V5, while the Holter ECG showed multifocal PVCs (922 per 24 h), isolated or organized, with both RBBB and LBBB morphologies, and an episode of nonsustained ventricular tachycardia (VT) of LBBB morphology. A cardiac MRI was performed, which showed normal indexed end-diastolic LV volume, an LV diameter close to the superior limit of the normal range, an LVEF of 52%, mild inferior and inferoseptal regional parietal hypokinesia, elevated RV indexed volume, systolic dysfunction, and regional dyskinesia of the RV free wall (Figure 1B).

According to the 2020 Padua criteria, the diagnosis of a biventricular variant of ACM was made. Given the positive family history and long QT intervals, genetic testing was performed. The results were negative for mutations specific to LQT1 and LQT2; however, a heterozygous VUS mutation in the TTN gene was positive. According to the 2023 guidelines of the European Society of Cardiology, we decided to implant a Medtronic Mirro MRI single-chamber cardioverter defibrillator (ICD) for primary prevention as a class IIa level B indication.[1]

CASE 3

A 13-year-old male adolescent, a former performance athlete, with a positive family history (one uncle diagnosed with Wolff–Parkinson–White syndrome, one with PVC with LBBB morphology, and one with hypertrophic cardiomyopathy), was diagnosed at the age of 12 with PVC

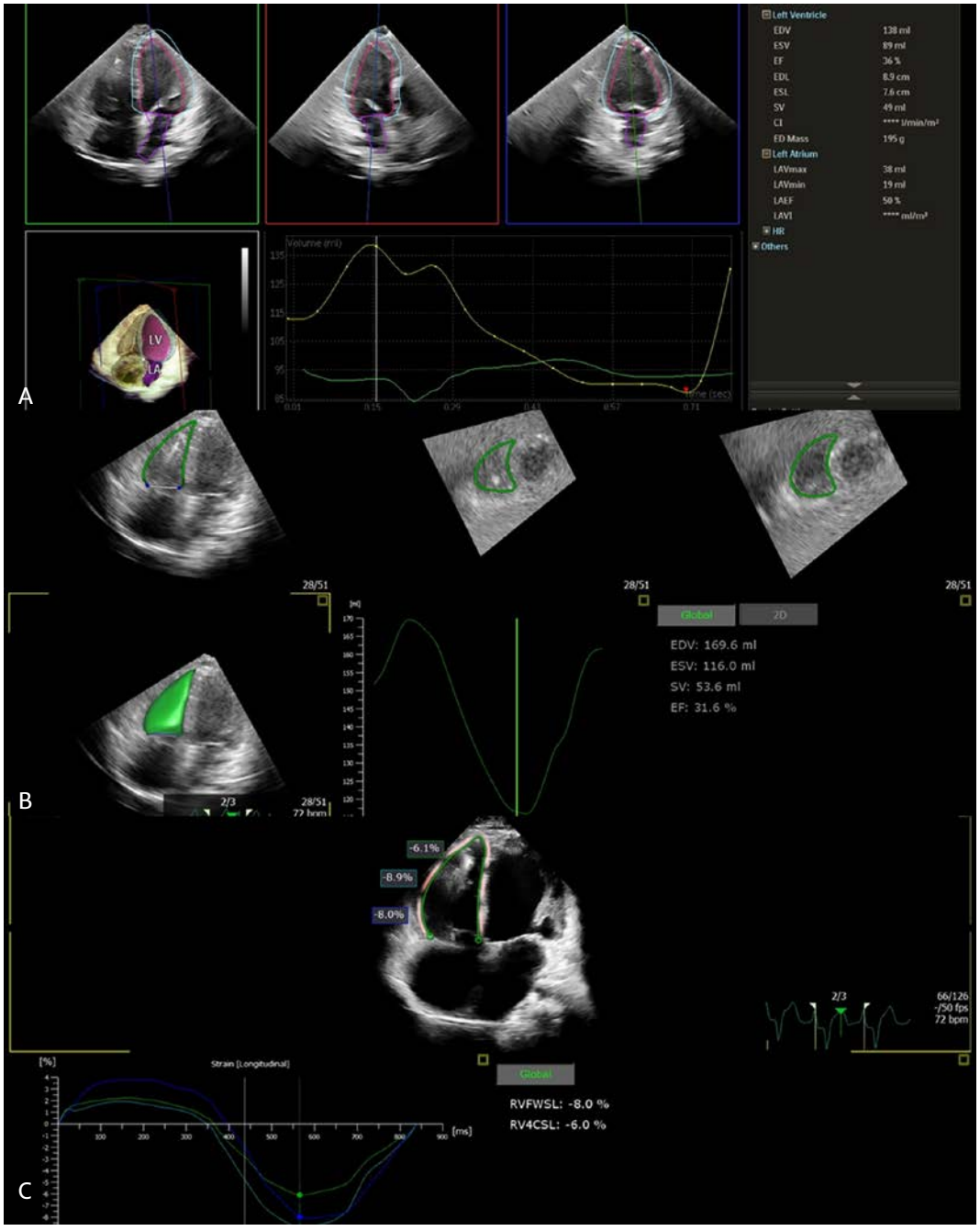

FIGURE 2. Quantification of LV and RV volumes and EF using 3D speckle-tracking analysis. **A.** Impaired systolic function of the LV with increased volumes. **B.** Elevated RV volumes and reduced RV EF. **C.** Illustration of RV strain measurement using speckle-tracking echocardiography showing impaired values of RV GLS and RVFW-LS. ESV, end-systolic volume; EDV, end-diastolic volume; SV, stroke volume. RV GLS, right ventricular global longitudinal strain; RVFW LS, right ventricle free wall longitudinal strain.

in repeating patterns (bigeminy, couplets) on a structurally normal heart, for which treatment with amiodarone was initiated.

Nine months later he suffered a cardiac arrest after an episode of ventricular fibrillation. The thoracic computed tomography (CT) scan revealed no signs of pulmonary embolism; however, it did reveal parietal hypertrophy of the LV wall and interventricular septum. Transthoracic echocardiography revealed regional RV hypokinesia, dyskinesia of RV free wall and RV apical aneurysm, whereas the MRI scan showed indexed RV volumes in the normal range, systolic RV dysfunction, with indexed LV volumes,

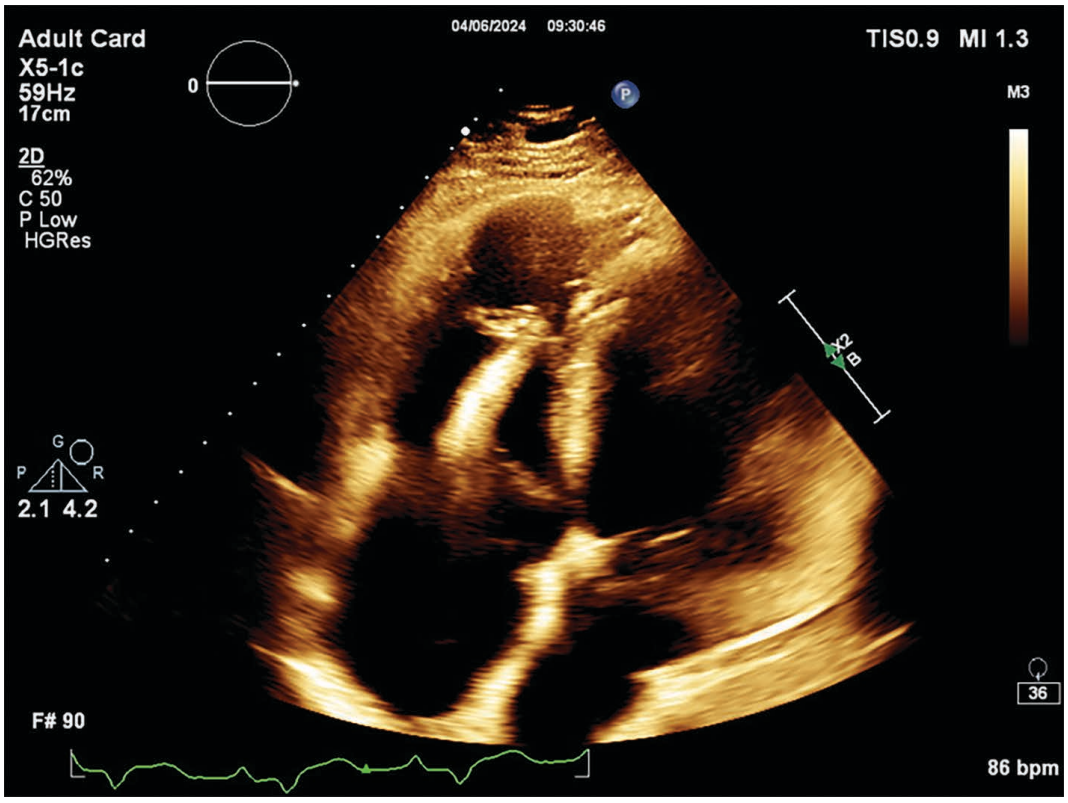

FIGURE 2. Apical 4-chamber view (2D) shows the dilated RV with an aneurysmal apex, and the ICD lead is visible.

LV diameter, LV systolic function, LV mass and wall thickness in the normal range, but with a depressed LV global longitudinal strain. The ECG revealed sinus rhythm, diffuse concave ST-segment elevation, negative T waves in V2–V5, and multiple isolated PVCs with LBBB morphology. Holter ECG showed multifocal PVCs (1,316 per 24 h), isolated or organized, with both RBBB and LBBB morphologies. Genetic testing was performed, revealing a positive heterozygous VUS mutation in the FLNC gene.

According to the 2020 Padua criteria, a diagnosis of dominant right ACM was made. In the context of a positive history of cardiac arrest, we decided to implant a Medtronic Mirro MRI dual-chamber ICD for secondary prevention as a class I level A indication.

CASE 4

We present the case of a 17-year-old teenager with a positive family history (maternal grandfather with SCD) and no notable personal medical history except for substance abuse (alcohol, smoking, etc.). In December 2021, following a respiratory infection, the patient began experiencing gradually worsening exercise intolerance. By January 2022, the patient had a syncopal episode with clonic seizures on the right side of the body. Additionally, the patient reported severe exercise intolerance, weakness, and extreme fatigue. Transthoracic echocardiography showed dilated cardiac chambers with severe biventricular systolic dysfunction and multiple intracavitary formations suggestive of thrombi in both ventricles (Figure 2). A thoracic CT angiography revealed cardiomegaly, images resembling thrombi in both ventricles and the pulmonary artery trunk, minimal right pleural effusion, and increased pericardial and pericholecystic fluid. The ECG revealed RBBB and left anterior fascicular hemiblock. Holter ECG monitoring detected PVCs, some with LBBB and others with RBBB morphology, along with episodes of polymorphic non-sustained VT. Cardiac MRI revealed severely dilated and impaired LV systolic function with global hypokinesia, subendocardial fibrotic lesions, and a dilated RV with increased indexed volume, accentuated trabeculae but preserved systolic function.

According to the 2020 Padua criteria, an ACM diagnosis was made. Genetic testing unveiled a desmoplakin mutation in the DSC2 gene (VUS) and heterozygous mutations in MTHFR C677T, factor V G1691A (Leiden), and homozygous PAI-1 4G/4G profile, indicating a thrombophilia risk. In line with 2023 guidelines, implanting an ICD was

reasonable, prompting the implantation of a Medtronic single-chamber cardiac defibrillator (Figure 3).

DISCUSSION

Arrhythmogenic right ventricular cardiomyopathy is a hereditary condition characterized by progressive deterioration of heart muscle, posing a significant risk of SCD and ventricular tachyarrhythmias. Although ARVC usually manifests between the ages of 30 and 40, the lack of comprehensive studies focusing on the pediatric population may contribute to underdiagnosis in this age group. It is estimated that around 15% of patients with ARVC experience symptoms during childhood, often presenting with a more severe phenotype and an increased risk of SCD.[3]

Recent updates to the Padua criteria introduced the concept of forms limited to the LV and emphasized the significance of fibrosis detected on MRI. Key innovations include late gadolinium enhancement at MRI as a major criterion and the consideration of isolated PVCs not only in terms of absolute number but also in terms of morphology.[2] In our cases, ACM was suspected in cases 3 and 4 using echocardiography. However, in the first two cases, only LV function was impaired, suggesting DCM. MRI proved to be a better diagnostic tool in these cases, as echocardiography did not reveal specific abnormalities of the RV. Conversely, there are ACM cases in which LV function remains normal, as seen in our third case. Despite a normal LVEF, LV global longitudinal strain was impaired. This finding aligns with a study by Chungsomprasong *et al*., which showed that most patients did not have decreased LVEF, but did exhibit impaired LV circumferential strain and strain rate on advanced echocardiography.[4]

The 12-lead ECG is a pivotal tool in diagnosing ACM. Research indicates that over 85% of patients meeting ACM diagnostic criteria display at least one characteristic ECG feature, although up to 12% may have a normal ECG.[5] ARVC is a progressive condition, evidenced by dynamic ECG changes over time. T-wave inversion in precordial leads, particularly in patients aged 14 years and older, serves as a major diagnostic abnormality in ARVC, as stated by the Padua criteria.[2] However, there were some concerns that in patients younger than 14 years old, T-wave inversion may represent a normal variant and should be cautiously interpreted in the absence of other clinical indicators. In our cases, all patients presented with T-wave inversion in precordial leads.

Various forms of cardiomyopathy, previously thought to be influenced by external factors, actually have genetic components. Genes associated with DCM or ARVC have been detected in 8–22% of adults and children who present with acute myocarditis. Therefore, for example, patients with desmosomal protein gene variants have a higher incidence of myocarditis recurrence and ventricular arrhythmias.[1] This finding suggests a potential link between genetic predisposition and disease severity in patients with myocarditis. Regarding ARVC, more than 50% of patients had pathogenic variants in major cardiac desmosome genes, with fewer having harmful mutations in non-desmosomal genes. However, further research is necessary to ascertain the harmful impact of VUS genes, which are present in phenotype-positive individuals as well, not only in symptomless and phenotype-negative patients. In a study by Mazzacarra *et al*., genetic testing revealed genes with VUS in almost 30% of patients, of which 85% in uncommon genes for cardiomyopathies.[6] Also, in all our cases, genetic testing revealed VUS mutations, although all cases fulfilled the Padua criteria for ACM. This finding emphasizes that monitoring these variants over time holds the potential to refine their classification, thereby offering novel perspectives for the management of carriers and their familial cohorts. Additionally, certain VUSs might serve as modifier genes, influencing clinical phenotypes and contributing to the observed clinical diversity within familial contexts. Furthermore, the identification of genetic variants associated with cardiomyopathy underscores the importance of genetic screening and counselling, especially for individuals with a family history of cardiac disease.

According to European guidelines, patients with ACM who exhibit extensive disease involving the LV, a family history of SCD, or undiagnosed syncope where VT or ventricular fibrillation has not been excluded as the cause of syncope, should consider ICD implantation (Class II, Level of evidence C).[7,8] In adult ACM cohorts, risk factors for SCD include ventricular arrhythmia-induced syncope, prolonged/non-sustained VT, and severe RV and/or LV systolic dysfunction. However, there is minimal information on SCD risk classification in pediatric patients. SCD affects 2–15% of young patients with ACM, and patients exhibiting SCD or prolonged ventricular arrhythmias have a class I indication for ICD implantation.[8] Although there is not enough data to support ICD placement for primary prevention in young patients with ACM, it is reasonable in cases of hemodynamically tolerated persistent VT, syncope likely caused by ventricular arrhythmia, or LVEF ≤35%. In our second case, the ICD was implanted owing to sustained episodes of VT in a symptomatic patient with a family history of SCD. In our third case, the ICD was implanted for secondary prevention of SCD, and in our last

case, the patient presented persistent VT with decreased LV systolic function.

CONCLUSION

In conclusion, ARVC continues to pose a significant challenge in pediatric populations owing to its variable presentation, potential for underdiagnosis, and associated risk of SCD. Diagnosing ACM in pediatric patients requires a comprehensive evaluation, including clinical assessment, ECG, echocardiography, MRI, and genetic testing. The lack of comprehensive epidemiological studies and standardized diagnostic criteria specific to pediatric populations highlights the need for further research. Additionally, continued efforts to improve risk stratification and establish guidelines for the management of pediatric ACM are essential to optimize patient outcomes and ensure timely interventions, including ICD placement when indicated.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

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REFERENCES

1. Arbelo E, Protonotarios A, Gimeno JR, et al; ESC Scientific Document Group. 2023 ESC Guidelines for the management of cardiomyopathies. Eur Heart J. 2023 Oct 1;44(37):3503-3626. doi: 10.1093/eurheartj/ehad194
2. Corrado D, Perazzolo Marra M, Zorzi A, et al. Diagnosis of arrhythmogenic cardiomyopathy: The Padua criteria. Int J Cardiol. 2020 Nov 15;319:106-114. doi: 10.1016/j.ijcard.2020.06.005
3. Smedsrud MK, Chivulescu M, Forså MI, et al. Highly malignant disease in childhood-onset arrhythmogenic right ventricular cardiomyopathy. Eur Heart J. 2022 Dec 1;43(45):4694-4703. doi: 10.1093/eurheartj/ehac485
4. Chungsomprasong P, Hamilton R, Luining W, Fatah M, Yoo SJ, Grosse-Wortmann L. Left Ventricular Function in Children and Adolescents With Arrhythmogenic Right Ventricular Cardiomyopathy. Am J Cardiol. 2017 Mar 1;119(5):778-784. doi: 10.1016/j.amjcard.2016.11.020
5. 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 Nov;16(11):e301-e372. doi: 10.1016/j.hrthm.2019.05.007
6. Mazzaccara C, Lombardi R, Mirra B, et al. Next-Generation Sequencing Gene Panels in Inheritable Cardiomyopathies and Channelopathies: Prevalence of Pathogenic Variants and Variants of Unknown Significance in Uncommon Genes. Biomolecules. 2022 Oct 3;12(10):1417. doi: 10.3390/biom12101417
7. Brugada J, Blom N, Sarquella-Brugada G, et al; European Heart Rhythm Association; Association for European Paediatric and Congenital Cardiology. Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEPC-Arrhythmia Working Group joint consensus statement. Europace. 2013 Sep;15(9):1337-82. doi: 10.1093/europace/eut082
8. Shah MJ, Silka MJ, Silva JNA, et al; Document Reviewers: Philip M. Chang, Fabrizio Drago, Anne M. Dubin, Susan P. Etheridge, Apichai Kongpatanayothin, Jose Manuel Moltedo, Ashish A. Nabar and George F. Van Hare. 2021 PACES expert consensus statement on the indications and management of cardiovascular implantable electronic devices in pediatric patients. Cardiol Young. 2021 Nov;31(11):1738-1769. doi: 10.1017/S1047951121003413