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EDITORIAL COMMENT

Pediatric-Onset Arrhythmogenic Cardiomyopathy

Look Right, Look Left, Look Both Ways*

Michael J. Ackerman, MD, PhD,[a,b,c] John R. Giudicessi, MD, PhD[d]

Arrhythmogenic cardiomyopathy (ACM) is an umbrella term used to describe a clinically and genetically heterogeneous group of heart muscle disorders characterized by prominent and potentially life-threatening ventricular and atrial arrhythmias as well as progressive fibrosis and/or fibro-fatty replacement of the ventricular myocardium (1). Classically, the prototypic subtype of ACM, arrhythmogenic right ventricular cardiomyopathy (ARVC), is viewed as a disease of the RV with only minor or late-onset involvement of the left ventricle (LV) (1). However, in recent years, the ACM clinical spectrum has grown to include both LV- (i.e., arrhythmogenic left ventricular cardiomyopathy [ALVC]) and biventricular-predominant patterns of disease as recognized formally by the recently released 2019 Heart Rhythm Society ACM expert consensus statement (2–6).

Once regarded as a disease of young adults (i.e., individuals in their third or fourth decade of life), a small, but growing, body of evidence has demonstrated that ACM can present during both childhood and adolescence (7,8). Although the frequency of strenuous exercise (9) and autoimmunity (e.g., presence of anti-desmoglein-2 antibodies) (10) have emerged as potentially important determinants of age-related penetrance and disease progression, the precise combination(s) of factors (genetic, environmental, and immunological) responsible for the clinical heterogeneity, incomplete penetrance, and variable expressivity that have come to define ACM clinically remain incompletely defined.

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Importantly, our current understanding of the epidemiology, clinical features, and natural history of ACM, including pediatric-onset disease (8), is derived primarily from ARVC-specific cohort studies. As such, the study by DeWitt et al. (11) in this issue of the *Journal* seeks to define the phenotypic spectrum present in pediatric-onset ACM through a systematic examination of the clinical phenotype (i.e., ventricular involvement, ventricular arrhythmia severity, presence of myocardial inflammation) and genetic underpinnings of patients presenting prior to age 21 years with a clinical history consistent with ACM.

Armed with the widely used 2010 ARVC task force criteria (12) and a set of proposed, but not yet validated, ALVC criteria (3), DeWitt et al. (11) demonstrate clearly that pediatric-onset ACM can involve predominantly the RV and/or LV at the time of presentation. Whereas ARVC was responsible for one-half (16 of 32; 50%) of pediatric-onset ACM, biventricular ACM and ALVC accounted for 28% (9 of 32) and 22% (7 of 32), respectively (11).

Of note, the genetic yield observed, across all 3 patterns of disease, in the pediatric-onset ACM study by DeWitt et al. (11) was considerably higher than that reported previously in adults (5). However, the

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From the [a]Department of Cardiovascular Medicine, Division of Heart Rhythm Services, Mayo Clinic, Rochester, Minnesota; [b]Department of Pediatric and Adolescent Medicine, Division of Pediatric Cardiology, Mayo Clinic, Rochester, Minnesota; [c]Department of Molecular Pharmacology and Experimental Therapeutics, Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, Minnesota; and the [d]Department of Cardiovascular Medicine, Clinician-Investigator Training Program, Mayo Clinic, Rochester, Minnesota. Dr. Ackerman is a consultant for Audentes Therapeutics, Boston Scientific, Gilead Sciences, Invitae, Medtronic, MyoKardia, and St. Jude Medical; and with the Mayo Clinic, he is involved in an equity and/or royalty relationship with AliveCor, Blue Ox Health Corporation, and Stemonix. Dr. Giudicessi has reported that he has no relationships relevant to the contents of this paper to disclose.

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genetic underpinnings of adult- and pediatric-onset ARVC, ALVC, and biventricular ACM appear to be somewhat similar (3,5). Consistent with prior ARVC studies (5,8), pathogenic and/or likely pathogenic (P/LP) variants in *PKP2*-encoded plakophilin-2 were responsible for the bulk of classic ARVC (14 of 16; 88%) and pediatric-onset ACM in general (17 of 32; 53%) (11). Similarly, P/LP variants in *DSP*-encoded desmoplakin and *LMNA*-encoded lamin A/C, genes associated strongly (*DSP*) or predominantly (*LMNA*) with arrhythmia-prone forms of dilated cardiomyopathy (13), were responsible for the majority of pediatric-onset ALVC cases (6 of 7; 86%; 3 P/LP variants in *DSP* and 3 P/LP variants in *LMNA*) (11). Lastly, >1 rare variant in a desmosomal gene (i.e., *PKP2*, *DSP*, *DSC2*, *DSG2*, and *JUP*), indicative of a potential homozygous or compound heterozygous state, was observed in the majority of children and adolescents with a biventricular presentation (6 of 9; 67%) (11). This aligns with prior work indicating that individuals with >1 putative ARVC-causative genetic variant present earlier in life and with more frequent LV involvement (5).

Although the patterns of ventricular involvement and observed genotype-phenotype correlations (i.e., *PKP2* in pediatric-onset ARVC, *DSP* and *LMNA* in pediatric-onset ALVC, and homozygosity/compound heterozygosity in pediatric-onset biventricular ACM) are intriguing, the study by DeWitt et al. (11) is not without limitations. Unlike the prior pediatric-onset ARVC study by Te Riele et al. (8), the absence of an adult-onset ACM comparison cohort in the study by DeWitt et al. (11) limits our ability to elucidate what factors, if any, differentiate pediatric- from adult-onset ACM at the clinical and/or molecular levels. This limitation is further compounded by the unavailability of data pertaining to established environmental modifiers, namely exercise, and clinical outcomes (i.e., the ability to determine cumulative event-free survival). Although the small number of pediatric-onset ACM patients (n = 32) in the study of DeWitt et al. (11) likely precludes assessment of these variables, the reader is still left wondering the following: 1) how the observed distribution of ventricular involvement in pediatric-onset ACM compares directly to adults evaluated using the same diagnostic scorecards; 2) whether exercise is a reproducible determinant of pediatric-onset ARVC and whether it influences *DSP*- and *LMNA*-mediated, ALVC age-related penetrance in an analogous fashion; and 3) whether clinical outcomes in pediatric-onset ACM are influenced by the ventricle(s) predominantly involved at the time of presentation. In addition, potentially important nondesmosomal genes that contribute to ACM pathogenesis, including 7 of 15 genes (47%) prioritized in the recent Heart Rhythm Society ACM consensus document (*BAG3*, *FLNC*, *LDB3*, *NKX2-5*, *PLN*, *RBM20*, and *SCN5A*) (6), were not assessed and could potentially explain the small number of cases that remain genotype-negative.

Nevertheless, the study by DeWitt et al. (11) represents an important step forward in the ongoing quest to raise awareness that ACM, in both children and adults, is truly a biventricular disease with clinically and genetically distinct right (ARVC), left (ALVC), and biventricular forms. Hopefully, the findings of DeWitt et al. (11) in concert with the guidance provided by the much needed 2019 ACM expert consensus statement (6) will encourage existing and future ACM studies and/or registries to enroll patients, of all ages, from across the entire ACM phenotypic spectrum (i.e., ARVC, ALVC, and biventricular ACM). With any luck, insights gleaned from future international and/or multicenter ACM registry-based studies will help improve our understanding of the environmental and genetic factors that predispose to all forms of pediatric-onset ACM and aid in the development of novel therapeutic approaches designed to prevent and/or slow the progression of these potentially life-threatening genetic heart diseases.

ADDRESS FOR CORRESPONDENCE: Dr. Michael J. Ackerman, Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory, Guggenheim 501, Mayo Clinic, Rochester, Minnesota 55905. E-mail: ackerman.michael@mayo.edu. Twitter: @MJAckermanMDPhD.

REFERENCES

1. Corrado D, Basso C, Judge DP. Arrhythmogenic cardiomyopathy. Circ Res 2017;121:784–802.

2. Norman M, Simpson M, Mogensen J, et al. Novel mutation in desmoplakin causes arrhythmogenic left ventricular cardiomyopathy. Circulation 2005;112:636–42.

3. Sen-Chowdhry S, Syrris P, Prasad SK, et al. Left-dominant arrhythmogenic cardiomyopathy: an under-recognized clinical entity. J Am Coll Cardiol 2008;52:2175–87.

4. van der Zwaag PA, van Rijsingen IA, Asimaki A, et al. Phospholamban R14del mutation in patients diagnosed with dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy: evidence supporting the concept of arrhythmogenic cardiomyopathy. Eur J Heart Fail 2012;14:1199–207.

5. Bhonsale A, Groeneweg JA, James CA, et al. Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/

cardiomyopathy-associated mutation carriers. Eur Heart J 2015;36:847–55.

6. Towbin J, McKenna WJ, Abrams DJ, et al. 2019 HRS Expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. Heart Rhythm 2019 May 9 [E-pub ahead of print].

7. Etoom Y, Govindapillai S, Hamilton R, et al. Importance of CMR within the Task Force Criteria for the diagnosis of ARVC in children and adolescents. J Am Coll Cardiol 2015;65:987–95.

8. 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.

9. James CA, Bhonsale A, Tichnell C, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. J Am Coll Cardiol 2013;62:1290–7.

10. Chatterjee D, Fatah M, Akdis D, et al. An autoantibody identifies arrhythmogenic right ventricular cardiomyopathy and participates in its pathogenesis. Eur Heart J 2018;39:3932–44.

11. 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.

12. 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.

13. Walsh R, Thomson KL, Ware JS, et al. Reassessment of Mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60,706 reference samples. Genet Med 2017;19:192–203.

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