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Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy in the Pediatric Population

Clinical Characterization and Comparison With Adult-Onset Disease

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ABSTRACT

OBJECTIVES The aims of this study were to determine the clinical characteristics and outcomes of pediatric-onset arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) and to compare these with those of adult-onset ARVD/C.

BACKGROUND Improved early detection and increased awareness of ARVD/C have led to a growing group of pediatric patients seeking management recommendations. Prior studies have mainly included adults with ARVD/C; however, clinical features and outcomes may differ in pediatric subjects.

METHODS Among 502 subjects fulfilling task force criteria for ARVD/C, we identified 75 (15%) with pediatric-onset disease (diagnosis at <18 years of age or probands presenting symptomatically at <18 years of age). Clinical characteristics and outcomes (sustained ventricular tachycardia, cardiac transplantation, and death) were compared between pediatric and adult patients.

RESULTS Pediatric patients presented at 15.3 ± 2.4 years of age. Most pediatric patients were male (55%) and ARVD/C-associated mutation carriers (80%). One-fourth of pediatric patients presented with sudden cardiac death (15%) or resuscitated sudden cardiac arrest (11%). Compared with adults, pediatric patients were disproportionately mutation carriers ($p = 0.002$) but not more often male ($p = 0.696$) or probands ($p = 0.371$). Pediatric patients were more likely to present with sudden cardiac death ($p = 0.003$), whereas adults more often presented with sustained ventricular tachycardia ($p = 0.017$). There were no other phenotypic differences between the groups. During 8.4 ± 7.5 years of follow-up, survival free from sustained ventricular tachycardia ($p = 0.359$), cardiac transplantation ($p = 0.523$), and death ($p = 0.359$) was similar between pediatric and adult patients.

CONCLUSIONS Pediatric patients with ARVD/C are typically male mutation carriers presenting in adolescence. Pediatric patients disproportionately present with sudden cardiac death. However, once diagnosed, clinical characteristics and outcomes are similar between pediatric and adult patients. (J Am Coll Cardiol EP 2015;1:551–60)

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ABBREVIATIONS AND ACRONYMS

ARVD/C = arrhythmogenic right ventricular dysplasia/cardiomyopathy

IQR = interquartile range

PVC = premature ventricular complex

SCA = sudden cardiac arrest

SCD = sudden cardiac death

TFC = task force criteria

VT = ventricular tachycardia

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an inherited cardiomyopathy characterized by fibro-fatty replacement of the right ventricular musculature, predisposing patients to ventricular arrhythmias and ventricular dysfunction (1). ARVD/C was once regarded as a disease most relevant to the young adult population, but the past decade has witnessed a growing group of children diagnosed with this disease. However, pediatric patients with ARVD/C are underrepresented in published research, with the largest series limited to only 23 patients (2). As such, few data are available to guide management recommendations in these young patients.

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The heterogeneity in the clinical expression of ARVD/C is well recognized (3). ARVD/C can be the cause of sudden cardiac death (SCD) as early as adolescence, but genetically predisposed subjects may remain without signs and symptoms until old age (4,5). Whether a difference exists in the presentation, clinical characteristics, and natural history of ARVD/C between pediatric and adult ARVD/C remains unknown. Moreover, the factors influencing age of disease onset in ARVD/C remain to be elucidated. Although recent data suggest that endurance exercise plays an important role in the pathogenesis of ARVD/C (6,7), the difference in exercise participation and its contribution to early presentation in pediatric compared with adult ARVD/C is as yet unknown. Therefore, we assembled a large and novel transatlantic cohort of children and adolescents with ARVD/C to describe the presentation, clinical characteristics, and outcomes of pediatric ARVD/C and compare these with those of adult ARVD/C. As a secondary aim, we sought to compare exercise participation in the formative adolescent years between children and adults with ARVD/C.

METHODS

STUDY POPULATION. The study population was identified from the Johns Hopkins ARVD/C registry and the University Medical Center Utrecht ARVD/C registry. Both registries prospectively enroll patients with ARVD/C and their family members with possible histories of the disease. For the purpose of this study, we included 502 subjects who had undergone genotype analysis and were diagnosed with ARVD/C on the basis of revised 2010 task force criteria (TFC) by last follow-up (8). Patients were considered pediatric if a definite ARVD/C diagnosis was established before the age of 18 years and/or if they were probands presenting with ARVD/C-related symptoms before the age of 18 years. All other subjects were classified as having adult ARVD/C. All registry participants provided informed consent, and the study protocol was approved by the respective institutional review boards.

CLINICAL CHARACTERIZATION. Participants were evaluated as described previously (9). The medical history of each patient was obtained by review of medical records, clinical evaluation, and/or patient interview. Detailed clinical information regarding demographics, presentation, symptom onset, and noninvasive and invasive tests was obtained for every participant. Twelve-lead electrocardiograms (recorded at rest, 10 mm/mV at a paper speed of 25 mm/s) were evaluated for repolarization (precordial T-wave inversion in leads V_1 and V_2 or beyond) and/or depolarization (epsilon waves or terminal activation duration ≥55 ms) criteria for ARVD/C. As per diagnostic TFC, precordial T-wave inversions were not taken into account for patients under the age of 14 years (8). Twenty-four-hour Holter monitors were evaluated for premature ventricular complex (PVC) count, which according to the 2010 TFC was regarded as abnormal if more than 500 PVCs were recorded. Signal-averaged electrocardiographic recordings, obtained using time-domain analysis with a bandpass filter of 40 Hz, were evaluated for evidence of late potentials using age-appropriate criteria (10). In addition, echocardiography, cardiac magnetic resonance imaging, and right ventricular angiography were reviewed to determine the severity and extent of structural abnormalities according to the 2010 TFC.

FOLLOW-UP AND OUTCOME MEASURES. Patient management was performed at the discretion of the

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