Arrhythmogenic cardiomyopathies in children – seek and you shall find

Juan Pablo Kaski[1,2]

[1]Centre for Paediatric Inherited and Rare Cardiovascular Disease, Institute of Cardiovascular Science, University College London, UK

[2]Centre for Inherited Cardiovascular Diseases, Great Ormond Street Hospital, London, UK

Address for correspondence

Dr Juan Pablo Kaski

Associate Professor of Paediatric Inherited Cardiology

Centre for Paediatric Inherited abd Rare Cardiovascular Disease

University College London Institute of Cardiovascular Science

Zayed Centre for Research into Rare Disease in Childhood

20 Guilford Street

London WC1N 1DZ

j.kaski@ucl.ac.uk

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a heritable heart muscle disorder characterised by ventricular arrhythmia and structural abnormalities of the ventricular myocardium, in the form of predominantly right ventricular (RV) dilatation and/or regional or global dysfunction and fibrofatty replacement of the myocardium histologically[1]. Over time, with the recognition of left ventricular involvement in many cases of ARVC, the paradigm has shifted from a focus on severe right ventricular disease (so-called "classical ARVC") to a broader spectrum that includes subclinical phenotypes, and biventricular or even left-dominant disease, leading to the concept of "arrhythmogenic cardiomyopathy" as an umbrella term that encompasses a range of diverse phenotypes and aetiologies[2]. The diagnosis of ARVC is based on the 2010 modified task force criteria (TFC), encompassing diagnostic information from a range of sources, including measures of RV dysfunction, histological abnormalities, electrocardiographic characteristics, ventricular arrhythmia of RV origin and evidence of familial disease or pathogenic variants in desmosomal genes[1].

With the exception of rare autosomal recessive cardiocutaneous syndromes such as Naxos disease[3] or Carvajal syndrome[4], which usually present in childhood, ARVC has traditionally been considered a disease of the young adult. This is based on the findings of family cohort studies suggesting that ARVC very rarely manifests in childhood and that sudden death is rarely reported in paediatric relatives[5,6]. Furthermore, there are concerns around the utility of the 2010 TFC in the paediatric population, given that T wave inversion in the anterior precordial leads is a normal finding in prepubertal children[7,8]. As a result, successive international guidelines have recommended that clinical screening for ARVC in first-degree relatives should not commence before the age of 10-12 years[9,10]. While there is no doubt

that there is an age-related penetrance to ARVC, with peak age at presentation between 30 and 40 years of age, the reality is that there have been no studies systematically evaluating the penetrance of ARVC in childhood, and paediatric populations are underrepresented in the medical literature, raising the possibility that *"if you don't look, you won't find"*. In this context, the paper by Smedsrud and colleagues[11] in this issue of the *Journal* represents a significant advance in our knowledge and understanding of childhood-onset ARVC, and has important implications for inherited cardiomyopathies more widely.

In their paper, Smedsrud *et al.* report the findings of 62 children (aged <18 years and including both affected individuals and heterozygous phenotype-negative carriers of a familial pathogenic variants) from a single national referral centre, of whom 32% (including 11 probands) fulfilled 2010 Task Force criteria for ARVC[11]. Importantly, 40% were diagnosed below the age of 12, and 23% of the total cohort suffered serious cardiac events (arrhythmic or transplantation/heart failure-related)[11]. Of note, 50% of events occurred in children under the age of 12 years[11]. These findings should not surprise us – over the last few years, there have been an increasing number of reports highlighting paediatric-onset disease associated with a high rate of sudden cardiac death[12] or transplantation[13] and a recognition that myocarditis, a relatively common clinical presentation in childhood, can be the initial manifestation of ARVC[14]. Indeed, there are data to suggest that up to 25% of sudden deaths in children and adolescents may be attributable to ARVC[15]. The paper by Smedsrud and colleagues[11] adds further to this body of knowledge, and for the first time in a systematic study of a paediatric population.

There are of course several limitations, including small numbers, potential for referral bias, a lack of age-specific normative data for some ECG parameters, and potential problems with the 2010 TF criteria for diagnosing ARVC in children. Furthermore, the cohort represents a "classical ARVC" cohort, with nearly 90% of patients harbouring a *PKP2* variant and all patients presenting with RV disease (with or without LV involvement), which is to be expected given that the entry criteria were fulfilment of the 2010 TF criteria. The findings may therefore not be generalisable to non-desmosomal disease (or even non-*PKP2*-related disease) or to predominantly LV phenotypes that fall under the umbrella term of arrhythmogenic cardiomyopathy. It may also be argued that this is a highly selected cohort, given that the probands are all affected children. However, less than one fifth of the total cohort were probands, and those diagnosed through family screening presumably included children where the index case in the family was an adult relative.

There will understandably be resistance to changing clinical practice that has been deeply embedded into disease paradigms for decades. Nevertheless, the findings of this study highlight that classical ARVC, at least, can present in young children, often with a very severe phenotype, and provide an argument for considering offering screening to children younger than 10-12 years, in contrast with current guidelines. And, of course, we have been here before. In hypertrophic cardiomyopathy (HCM), there has been a long-held view that clinical screening should not commence before the age of 10-12[9], but there is now compelling evidence to support screening for HCM in preadolescent children[16,17], as acknowledged in the most recent AHA/ACC guidelines for HCM, where screening is now recommended at the time when HCM is diagnosed in another family member, regardless of the child's age[18]. There is therefore now substantial data emerging to challenge existing

paradigms of disease across a range of inherited cardiomyopathies, including now ARVC[11], particularly in relation to the age at which screening should commence **(Graphical abstract)**. Key to this paradigm shift is the demonstration that significant disease exists in preadolescents with genetic cardiomyopathies. The next question is whether early identification can result in improved outcomes for this group of patients. As we move into an era of exciting new therapeutic opportunities in the field of cardiomyopathies, it is ever more important to ensure that children are at the forefront and adequately represented, both in natural history studies and in clinical trials. Systematic studies in childhood of disease expression and progression are a major first step towards this.

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