

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary heart muscle disorder that affects between 1 in 1000 to 5000 adults [1]. It is characterised by myocardial apoptosis and fibrofatty replacement in the subepicardial layers of the right ventricular myocardium, but it is well established that the same pathology can affect both ventricles or predominantly the left ventricle. ARVC usually manifests between the second and fourth decade of life but can present during adolescence [2]. Early symptoms include palpitations, syncope and at later stages patients may develop heart failure. Sudden cardiac death (SCD) can occur at any age but is most common during early adulthood. ARVC is typically inherited as an autosomal dominant trait predominantly caused by mutations in genes encoding a number of key desmosomal proteins. Phenotypic variability, even among carriers of the same gene mutations is common and makes diagnosis and management the condition very challenging. Factors such as exercise and sex have been advocated as phenotypic modifiers [3, 4].

Ever since the first reports of the disease, inflammatory cell infiltrates have been described in patients diagnosed with ARVC at post mortem, with the highest prevalence in people with more diffuse disease[5]. The subepicardial distribution of typical lesions is very similar to that reported in classical myocarditis and on many occasions patients with ARVC seek medical attention with symptoms of chest pain and palpitations accompanied by electrocardiographic changes and cardiac biomarkers consistent with myocarditis. These so called “hot-phases” can be the initial presentation of ARVC and correlate with changes in ventricular morphology and function [6, 7]. In vivo data on cardiac inflammation using non-invasive imaging in AC are limited but cardiac magnetic resonance (CMR) imaging often demonstrates patterns of scarring reminiscent of those seen following myocarditis.

In this edition of the journal, Martins and colleagues present a case series of six children presenting with myocarditis-like episodes associated with ARVC [8]. Most presented with symptoms including chest pain, palpitations and pre-syncope and were found to have elevated cardiac troponin levels. Only one had ST-segment deviation on the ECG but all had abnormal CMR scans with evidence of myocardial hyperaemia and capillary leak as demonstrated by early gadolinium enhancement and myocardial fibrosis. Four of the six had T2 hyperintensity suggestive of myocardial oedema. Importantly, all cases had evidence of biventricular involvement. In most cases this was the first manifestation of disease.

The youngest patient was only two years old and had a very malignant disease course with severe LV impairment that led to refractory cardiogenic shock and death. Notably, this patient was homozygous for a truncating desmoplakin gene mutation. Another patient who was heterozygous for a truncating desmoplakin mutation presented aged 5 years and was transplanted after one year. Follow-up of the remaining cases revealed disease progression in the form of new ECG and imaging abnormalities.

Although there have been isolated reports in the past[7], this is the first case series of patients with paediatric ARVC presenting with hot-phases[8]. The size of the study population is too small to make definitive conclusions about genotype, clinical characteristics and prognosis in childhood ARVC but the association between structural gene abnormalities and clinical myocarditis may have wider implications for adult and paediatric cardiology.

One can only speculate about the mechanisms that underlie these genetically predisposed myocarditis episodes. Infection has been considered as a cause of the inflammatory infiltrates observed in cardiac autopsies of patients with ARVC, but no convincing causative relationship has been demonstrated [1]. Auto-immunity is another possible explanation and the disease behaves similarly to classic autoimmune disease with flares and periods of stability. Glycogen synthase kinase-3 beta (GSK3-b) a regulator of both the innate and adaptive immune system, has been recently implicated in the pathogenesis of ARVC [9, 10].

There are few data on ARVC in children, but this is a critical period in the disease as it is during adolescence and young adulthood that the first manifestations usually appear. As quoted by many famous diagnosticians “you only see what you look for and you only recognize what you know”. The worlds of myocarditis and cardiomyopathy seem to be distant and unrelated but ARVC is emerging as a pathology in which genetic and inflammatory pathways conspire to cause disease. A systematic approach to the characterization of hot-phase episodes is necessary to better understand the role of inflammation in ARVC and to facilitate discovery of novel therapeutic targets.

## References

- [1] Basso C, Corrado D, Marcus FI, Nava A, Thiene G. Arrhythmogenic right ventricular cardiomyopathy. *Lancet*. 2009;373:1289-300.
- [2] Te Riele A, James CA, Sawant AC, Bhonsale A, Groeneweg JA, Mast TP, et al. Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy in the Pediatric Population: Clinical Characterization and Comparison With Adult-Onset Disease. *JACC Clin Electrophysiol*. 2015;1:551-60.
- [3] Sawant AC, Bhonsale A, te Riele AS, Tichnell C, Murray B, Russell SD, et al. Exercise has a disproportionate role in the pathogenesis of arrhythmogenic right ventricular dysplasia/cardiomyopathy in patients without desmosomal mutations. *J Am Heart Assoc*. 2014;3:e001471.
- [4] Akdis D, Saguner AM, Shah K, Wei C, Medeiros-Domingo A, von Eckardstein A, et al. Sex hormones affect outcome in arrhythmogenic right ventricular cardiomyopathy/dysplasia: from a stem cell derived cardiomyocyte-based model to clinical biomarkers of disease outcome. *European heart journal*. 2017;38:1498-508.
- [5] Campuzano O, Alcalde M, Iglesias A, Barahona-Dussault C, Sarquella-Brugada G, Benito B, et al. Arrhythmogenic right ventricular cardiomyopathy: severe structural alterations are associated with inflammation. *Journal of clinical pathology*. 2012;65:1077-83.
- [6] Patrianakos AP, Protonotarios N, Nyktari E, Pagonidis K, Tsatsopoulou A, Parthenakis FI, et al. Arrhythmogenic right ventricular cardiomyopathy/dysplasia and troponin release. Myocarditis or the "hot phase" of the disease? *International journal of cardiology*. 2012;157:e26-8.
- [7] Mavrogeni S, Protonotarios N, Tsatsopoulou A, Papachristou P, Sfindouraki E, Papadopoulos G. Naxos disease evolution mimicking acute myocarditis: the role of cardiovascular magnetic resonance imaging. *International journal of cardiology*. 2013;166:e14-5.
- [8] Martins D, Ovaert C, Khraiche D, Boddaert N, Bonnet D, Raimondi F. Myocardial inflammation detected by cardiac MRI in Arrhythmogenic right ventricular cardiomyopathy: A paediatric case series. *International journal of cardiology*. 2018.
- [9] Beurel E, Michalek SM, Jope RS. Innate and adaptive immune responses regulated by glycogen synthase kinase-3 (GSK3). *Trends Immunol*. 2010;31:24-31.
- [10] Chelko SP, Asimaki A, Andersen P, Bedja D, Amat-Alarcon N, DeMazumder D, et al. Central role for GSK3beta in the pathogenesis of arrhythmogenic cardiomyopathy. *JCI insight*. 2016;1.