Invited editorial: Childhood-onset hypertrophic cardiomyopathy research coming of age

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Hypertrophic cardiomyopathy (HCM) is a heart muscle disorder that can affect individuals of all ages, but, due to age-related penetrance, is much rarer in children than in adults (estimated prevalence ~3 per 100,000 compared to 1 in 500). For decades, much of the published data on childhood-onset HCM were derived either from small, highly-selected single-centre reports or from population-based studies. As a result, childhood HCM was seen as being primarily the result of inborn errors of metabolism, malformation syndromes or neuromuscular disorders, and usually associated with a poor prognosis, with reported sudden cardiac death (SCD) rates 5-fold higher than those seen in adults. Familial disease was rarely reported and sarcomere protein gene variants were thought to be very rare. This view of childhood-onset HCM as a distinct entity to that seen in adults was reflected in successive European and North American HCM guidelines, where clinical and genetic screening has not been routinely recommended below the age of 10 or 12. The last decade, however, has seen a shift in our understanding of childhood HCM. Pathogenic variants in the sarcomere protein genes are now recognised to be the commonest cause of HCM in all age groups beyond infancy and recent collaborative studies have shown that SCD rates are in the region of 1-2% per year, more in line with adult HCM data. In the last year, two studies, from the UK and Canada, have challenged the notion that screening should not be offered routinely to children under the age of 10-12. Indeed, the 2020 American Heart Association/American College of Cardiology HCM guidelines no longer recommend a lower age limit for clinical screening of first-degree relatives of individuals with HCM.

The report by Marston and colleagues in this issue of the Journal is a further important step in the journey to understanding childhood-onset HCM. Here, the authors present data
from the Sarcomeric Human Cardiomyopathy Registry (SHaRe) on 1128 individuals with HCM diagnosed between 1 and 18 years of age, and compare these with 184 patients with infant-onset HCM (within the first year of life) and 6365 patients with adult-onset HCM (> 18 years). This represents the largest reported cohort of nonsyndromic childhood-onset HCM published to date, and a major strength is the availability of genetic data in over half of the cohort. The study has some important limitations, including the potential for both selection and survival bias, with approximately 60% of the childhood-onset patients originating from adult HCM centres. However, the fact that the median time from diagnosis to first assessment at a SHaRe site was just over 2 years is reassuring, and the authors’ findings are an important contribution to the field, providing novel insights into the natural history of childhood-onset HCM.

**Childhood-onset HCM is a disease of the sarcomere**

The finding that 63% of children who had undergone genetic testing had a pathogenic variant in one or more sarcomere protein genes confirms irrefutably that childhood-onset HCM is a disease of the sarcomere. In addition, the confirmation that ventricular arrhythmia is the most common adverse cardiac event during childhood highlights the importance of accurate risk stratification in this population\textsuperscript{11,12}, although it is notable that childhood-onset sarcomeric disease also appeared to be associated with an increased need for mechanical support for heart failure. Importantly, there appears to be an age-related difference in phenotypic expression of sarcomeric HCM, with childhood-onset HCM associated with heart failure outcomes and adult-onset HCM associated with a higher risk of atrial fibrillation.
The authors suggest that infant-onset HCM may represent a different disease process to both childhood and adult-onset HCM, and rightly argue that it should be considered as a separate entity both in clinical practice and in a research setting. Importantly, however, a similar proportion of those with infant-onset HCM had sarcomere protein gene variants as those with adult-onset disease (>40%), implying that the differences may not be related to the underlying aetiology, but, rather, related to disease expression. The findings in this group confirm a poor prognosis early on, but suggest that, for those infants who survive the first year of life, the outcomes are then better than those with childhood onset disease. This is also consistent with previously reported clinical experience of sarcomeric HCM diagnosed in infancy as a result of family screening\(^7\). Together, these findings highlight the importance of considering sarcomere protein gene mutations as a cause of HCM in all age groups, including infancy. Future studies to explore the role of genetic, epigenetic and environmental influences on phenotype expression are needed.

**Childhood-onset HCM is associated with progression to heart failure and atrial fibrillation**

A major finding from this study is the high frequency of atrial fibrillation and heart failure from the second decade of follow-up onwards in patients with childhood-onset HCM. This echoes previous reports from SHaRe highlighting the substantial lifelong burden of morbidity\(^13\) and extends this to the paediatric population. The findings also confirm that childhood-onset disease has a worse prognosis than adult-onset HCM, but, whilst initial reports from small, highly selected cohorts, had suggested SCD rates of up to 7% per year in childhood, the current study suggests that the poorer long-term outcomes are related to disease progression rather than arrhythmic events. The implications of this are significant. Current management strategies for HCM are focussed on symptom palliation, the
identification of at-risk relatives through family screening, and the prevention of disease-related complications, in particular SCD. However, none of these strategies are likely to have a significant impact on the burden of disease morbidity in the long term. The fact that there is a time lag between diagnosis and disease progression opens up unique opportunities for disease-modulating interventions, particularly in children (Figure). The field of HCM is now entering the era of personalised medicine, with the advent of gene therapy programmes \(^{14}\) and a focus on treatments targeting the underlying pathophysiology \(^{15}\). Preclinical data suggesting that small molecule myosin inhibitors may attenuate or even prevent disease expression \(^{16}\) provide cause for optimism, and nowhere more so than for childhood-onset HCM. An international collaborative approach involving basic, translational and clinical science is now needed to characterise disease expression and progression and develop novel therapies for childhood HCM.
Figure: Natural history of childhood-onset HCM and opportunities for disease-modifying interventions
References


