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Title: Hypertrophic Cardiomyopathy: A lifelong disease requiring lifelong treatment

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Hypertrophic Cardiomyopathy: A lifelong disease requiring lifelong treatment

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“The first patient to have surgical treatment (back in 1958) was a young man in whom the late Paul Wood had clearly identified the features of functional dynamic left ventricular outflow tract obstruction. He survived into middle age, with gradual reduction in wall thickness, loss of systolic efficiency, and relative dilatation of the previously small left ventricular cavity, and died in congestive failure from what is now recognised to be a progressive myopathy.”

Celia Oakley, 1995¹

Depending on one’s sense of national pride and knowledge of medical history, the first description of hypertrophic cardiomyopathy (HCM) can be attributed to any number of great anatomists and physicians working from the 17th Century onwards. The modern era for HCM is often said to have begun with Donald Teare’s landmark paper of 1958² that triggered (or perhaps coincided with) a period of intense clinical investigation which has continued unabated to the present day. The fruits of this collective endeavour include much progress in the management of HCM, particularly with respect to the prevention of sudden cardiac death and the treatment of left ventricular outflow tract obstruction. However, as the quote from Celia Oakley suggests¹, the focus on immediate clinical issues such as the need for implantable cardioverter defibrillators and intervention for disabling symptoms caused by outflow tract obstruction has meant that the long-term consequences of the myocardial disease have been somewhat neglected.

In this edition of the journal, investigators from North America and Europe have joined forces to help redress this imbalance. Using data from almost 5000 patients, The Sarcomeric Human Cardiomyopathy Registry (SHaRe) investigators report the cumulative incidence of clinically relevant endpoints including death, cardiac arrest, cardiac transplantation, appropriate implantable cardioverter-defibrillator (ICD) therapy, atrial fibrillation, stroke and progressive heart failure³. They show that for patients diagnosed at a young age (<40 years), the cumulative incidence of the overall composite endpoint was a remarkable 77% by the age of 60. For individuals first diagnosed over 60 years of age (a threshold previously suggested to convey a favorable prognosis), the cumulative incidence was lower, but still relevant to a third of patients. In a subgroup analysis, they also showed that patients with

pathogenic or likely pathogenic sarcomere protein gene mutations (the most common etiological subset of HCM) had a two-fold greater risk for adverse outcomes compared to patients without mutations.

Some contemporary outcomes studies suggest that when managed in accordance with clinical practice guidelines, the prognosis for most patients with HCM is relatively benign⁴. However, the demonstration in SHaRe of a high cumulative burden of disease morbidity and mortality is consistent with other data from diverse cohorts from around the World^{5,6}. Large observational studies such as SHaRe are of course subject to numerous potential biases that can impact on the validity and generalizability of their findings. One of the most important is survivor bias, in which patients who live longer are more likely to be enrolled in studies or to receive treatment than patients who die early. The potential for this bias in SHaRe is substantial given the analysis of events from birth. This type of analysis also assumes that patients are at risk of an event when in fact they are not (for example in childhood)—so called immortality bias. A consequence of this approach is that the frequency of adverse events in patients with a HCM phenotype may be underestimated as suggested by a recent analysis of national electronic health records in which the excess risk of preventable complications such as sudden cardiac death, thromboembolism and heart failure was substantial and a cause for concern⁷.

With respect to genotype, the SHaRe data confirm previous studies showing that carriage of a positive sarcomere mutation is associated with higher mortality⁸ but also demonstrate that this excess risk extends to the global burden of complications. In part this association was explained by the earlier onset of disease in mutation carriers, but the relationship persisted even when the model was adjusted for age. While the fact that the presence or absence of a mutation by itself is associated with adverse outcomes is important, it is very likely that individual mutations, by virtue of their different impact on protein function, structure and interactions, have a similarly variable effect on disease severity⁹. To model such complex interactions, it is necessary to have many more informative end-points in genotyped patients and better understanding of the contribution of genotype on prognostic modelling will inevitably require even larger curated data-sets.

An intriguing and potentially very important finding in this study is the association between genetic variants of unknown significance (GVUS) and prognosis. The identification of GVUS is increasing with the transition of genotyping into everyday clinical practice. To ensure consistency and reliability of genetic test reports, criteria for determining pathogenicity of genetic variants are necessarily stringent, but the findings in this study clearly imply that some variants currently classified as benign are in fact relevant to the disease phenotype. As the authors suggest, one take home message is that analytic pipelines require continuing refinement; it is also important that data on GVUS are carefully matched to prospective clinical data to ensure flexibility in classification and interpretation of genetic information in the future.

Discovery of novel treatments is not easy in common disorders let alone in diseases such as HCM where small patient numbers, long natural histories and disease heterogeneity all pose challenges to conventional drug discovery. Nevertheless, there are signs that we are on the threshold of a new and exciting chapter in the story of HCM and other cardiomyopathies. Characterization of sarcomere gene mutations has yielded insights into the earliest biomechanical defects that link pathogenic variants to cardiac remodeling and has suggested new targets for therapy (10). For example, hyperdynamic ventricular contraction and diastolic dysfunction are the earliest identified biomechanical defect in some MYH7 (β -myosin) mutations. The drug Mavacampten (MYK-461, Myokardia, San Francisco, CA, USA) is a small-molecule allosteric myosin inhibitor that restores contractile balance by decreasing adenosine triphosphatase activity in the cardiac β -myosin heavy chain (11). A phase 2a study evaluating the efficacy, safety and tolerability of Mavacampten in subjects with symptomatic HCM and LVOT obstruction ([NCT02842242](#)) is complete and a large Phase 3 study is due to start in 2018. Other promising approaches to mutations in other genes include drugs that reduce Ca^{2+} -sensitivity and/or recoup the relationship between troponin I phosphorylation and Ca^{2+} -sensitivity [12] and the use of gene therapies in myosin binding protein C [13].

The notion that prognosis for most patients with HCM is relatively benign is proving to be an oversimplification which understates the long term needs of many patients. The time has come for investigators, research funders and the Pharma industry to redouble their efforts

to understand the mechanisms of disease progression and to develop new and effective treatment strategies.

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