Lessons from rare cardiomyopathies: the importance of a phenotype-based approach to arrive at a specific diagnosis

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The cardiomyopathies are disorders of the heart muscle, characterised by structural and functional abnormalities in the absence of haemodynamic conditions that solely explain the observed myocardial abnormality[1]. Since the first formal consensus on classification in 1980[2], cardiomyopathies have been defined according to their morphological and physiological characteristics (e.g. ventricular hypertrophy or dilatation). More recent iterations have taken into account significant advances in our understanding and knowledge of the causes of cardiomyopathies by subdividing the morphological subtypes into familial/genetic and non-familial/non-genetic causes, but current classification schemes remain very much rooted in the identification of a clinical phenotype as the first step in the diagnostic pathway. There are good reasons for this, not least that, when a patient presents to the consulting room or emergency department, they present with clinical signs and symptoms suggesting a clinical phenotype, rather than with a genetic result (although the latter will likely become more common as commercially-available genetic testing becomes more popular); furthermore, although substantial strides have been made in our understanding of the aetiological basis of the cardiomyopathies, a significant proportion of cases remain gene-elusive, limiting the utility of a pure aetiological classification. On the other hand, with increasing availability and knowledge of the genetic (and non-genetic) causes of heart muscle disease, it is clear that arriving at a specific molecular diagnosis has important implications for the assessment and management of cardiomyopathies, both in the patient and in their relatives. This phenotype-based approach to reach a specific molecular diagnosis is the ultimate goal of the so-called “cardiomyopathy mindset”[3] and, nowhere is this approach more important than when dealing with rare cardiomyopathies.

In this issue of the *Journal*,[4] the Cardiomyopathies Working Groups of the Italian Society of Cardiology and the Italian Society of Pediatric Cardiology present a Position Statement on diagnosis and management of rare cardiomyopathies in adult and paediatric patients. Maintaining the phenotype-based approach, the authors systematically summarise the available evidence and provide practical recommendations for the diagnosis and management of specific cardiomyopathies that encourage practicing cardiologists and allied health professionals to consider how best to investigate and treat patients of all ages with rare (and not so rare) presentations of heart muscle disease. They should be commended on a gargantuan task, the result of which is the first comprehensive set of recommendations for rare diseases that, up until now, have been largely confined to short subsections and appendices in previous formal guidelines. Importantly, the recognition of many of these rare diseases, and their timely and accurate diagnosis, has the potential to significantly impact on patient care, with the availability of disease-specific therapies (e.g. enzyme replacement therapy for many inborn errors of metabolism and storage disorders, tafamidis for

amyloidosis, MEK inhibition in RASopathies). There will inevitably be disagreements around specific recommendations and many are based on very limited evidence, necessarily representing primarily consensus opinion of an expert group, but this statement is very timely and should act as a stimulus for further work in the field of rare cardiomyopathies.

More urgently, this position statement highlights important aspects that go beyond the rare cardiomyopathies. Central to the position paper is the recognition of the importance of an expert, multidisciplinary team in the assessment and management of cardiomyopathies. While this is particularly relevant in the context of rare, multisystem diseases such as those that are the focus of this position statement, the concept of a multidisciplinary approach to evaluation and treatment should be considered a key aspect of the management of all cardiomyopathies, even those that are more commonly recognised. Another important aspect of the position statement is the focus on both children and adults – we are dealing with conditions that can affect individuals and families across the lifecourse, yet most previous guidelines and consensus documents focus primarily on adult cardiomyopathies. While some cardiomyopathies are clearly diseases of childhood (e.g. Pompe disease) or adulthood (e.g. ATTR), there is increasing evidence that in most heart muscle disorders, even the “common” non-syndromic disorders traditionally thought to be of adult-onset, childhood presentation frequently occurs and can be associated with poor clinical outcomes[5]. The need, therefore, to consider heart muscle disorders as disease entities encompassing paediatric and adult populations is an important lesson for all cardiomyopathies.

As we enter an era of disease-specific therapies for cardiomyopathies, both common and rare, the need for a systematic, multidisciplinary, and expert approach to evaluation and management across the lifecourse has never been greater.

References

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