Rare diseases hiding in the cardiomyopathy clinic - the importance of seeing and observing

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“You see, but you do not observe.” (Sherlock Holmes - A scandal in Bohemia)

Mitochondrial disorders are clinically and genetically heterogeneous disorders characterised by multi-system involvement, particularly affecting organs with a high energy demand such as the heart. Most cases are caused by nuclear DNA mutations encoding components of the mitochondrial respiratory chain, inherited as autosomal dominant, recessive or X-linked traits. A significant minority, however, are due to maternally-inherited mutations in the mitochondrial DNA (mtDNA), and it is these disorders that typically present with a constellation of signs and symptoms involving several organ systems to varying degrees. Importantly, cardiac involvement, often in the form of hypertrophic cardiomyopathy (HCM), can be the first, or only, clinical manifestation of mitochondrial disease(1). MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes) syndrome is one such disorder, caused by mtDNA mutations affecting transfer RNA and associated with HCM (often progressing to an end-stage dilated, hyopokinetic phase), ventricular pre-excitation and conduction disease.

In this issue of the *Journal*, Brambilla and colleagues present the clinical profile and cardiovascular findings in a cohort of 21 children and adults from 10 different families with MELAS syndrome, evaluated over a period of 16 years(2). Cardiac involvement was identified in 8 individuals, representing just under 40% of patients, and consisting primarily of non-obstructive HCM but including also dilated cardiomyopathy and pulmonary hypertension. Of note, there were no cardiac events seen in the 5 patients diagnosed in adulthood, whereas the 3 children presenting with childhood-onset cardiomyopathy all died before the age of 30 years. Death in these patients was not cardiac, implying that the presence of early onset of cardiac involvement was a marker of overall disease severity, if not necessarily the major determinant of mortality in these 3 patients. These findings are in keeping with previous reports of childhood mitochondrial cytopathy, in which those children with cardiomyopathy were found to have substantially worse prognoses that those without, although the case of death in most of these individuals was indeed cardiac disease(3). These discrepancies highlight the difficulty in identifying prognostic markers in very rare diseases. Although the retrospective nature of the study did not allow assessment of the degree of heteroplasmy, which is likely to play a role in the difference observed between paediatric and adult onset disease, this “bimodal” distribution of disease onset is seen in other, more common, forms of paediatric heart muscle disease, including sarcomeric HCM, suggesting

that other factors, including potential genetic and epigenetic modifiers, may play a role in disease expression, regardless of aetiology(4).

Perhaps the most important message from Brambilla's paper is the finding that, in most cases, the diagnosis of MELAS syndrome was made by the cardiologists, often many years after the onset of multi-system symptoms, and despite the fact that clinical clues suggesting an underlying mitochondrial disorder had been present for many years prior. The use of basic clinical tools (family pedigree, basic laboratory investigations, the 12-lead electrocardiogram, transthoracic echocardiography), widely available and in every-day practice in all cardiology clinics, to identify red flags that point towards a specific aetiological diagnosis(5) should be a cornerstone of the evaluation of heart muscle disease both in paediatric and adult practice. As demonstrated by the authors in the context of MELAS syndrome, applying this approach in a cardiomyopathy setting is likely to unearth many rare diseases lurking within the large group of children and adults with heart muscle disease (and other cardiac disorders). Establishing a precise aetiological diagnosis a enables the clinician to provide a personalised approach to investigations, management strategies and counselling on the future course of disease and implications for the wider family, allowing targeted therapy and logical choice of tests, including molecular genetic analysis. Specific therapies are already available for many rare diseases (e.g. enzyme replacement therapy for infantile Pompe disease(6), MEK inhibition for infants with mutations in the RAS-MAPK pathway genes(7)), and this is certain to extend to more common conditions; novel small molecules targeting actin-myosin binding have already shown promise in preventing phenotypic disease expression in animal models of sarcomeric HCM(8) and have entered Phase III clinical trials in symptomatic adults with HCM.

As our knowledge of the genetic basis of disease widens and genotype-phenotype correlations grow, it becomes increasingly important to develop accurate diagnostic algorithms for disease. In this context, the importance of clinical acumen in directing a clinician to perform the required initial investigations should not be lost.

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