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Cardiomyopathy in Children Identifying the Causes*

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Trainees in pediatrics frequently hear the adage “children are not just small adults,” which serves as a reminder that diseases that are well described in adults can manifest differently in children, where chronological age and developmental stage affect disease presentation and recognition. In addition, the underlying causes of disease in children may differ from adults. Nevertheless, medical management and therapy are frequently adapted from adults, a population in which clinical trials are more readily performed. This is true for the treatment of heart failure in children, regardless of whether it results from congenital heart disease or cardiomyopathy (1,2). A challenge to the field is to develop therapies that are better tailored to the underlying cause of disease.

In children, cardiomyopathy is a rare disease that occurs in 1 to 2 individuals per 100,000 (3–6). It is genetically heterogeneous and can occur in the context of disorders of metabolism and energy production, neuromuscular disease, or genetic syndromic conditions (7,8). These 3 categories typically have other systemic features of disease, although cardiomyopathy may be the only feature at presentation. Pathogenic variants in genes encoding structural components of heart muscle represent a fourth etiology in children and cause isolated autosomal dominant cardiomyopathy in adults. The identification of shared genetic causes in children and adults highlights the intrafamilial variability in disease expressivity (9,10).

It is important to distinguish children with isolated cardiomyopathy from those with systemic disease because there are additional management considerations and medical needs in the latter population. There is some hope that etiology-specific therapies will emerge. For example, rapamycin has been proposed as a treatment for hypertrophic cardiomyopathy in RASopathies such as Noonan syndrome (11). Recently, a rapamycin analog was used successfully as a bridge to transplantation in an infant with Noonan syndrome with multiple

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lentigenes, severe cardiomyopathy, and a pathogenic variant that was previously associated with rapid heart failure in infancy (12). Furthermore, as a genetic disease, a diagnosis of cardiomyopathy in a child has specific implications for parents' and siblings' health management and cardiac surveillance. Precise recommendations for family members require identifying the genetic cause in the child.

Understanding the genetic landscape of pediatric cardiomyopathy has been difficult. One challenge has been the lack of comprehensive genetic evaluation and testing in this patient population to establish reliable estimates of the prevalence of isolated disease versus cardiomyopathy associated with other systemic features, so called "phenocopy conditions" not yet manifest due to age. Although guidelines for genetic evaluation and genetic testing in cardiomyopathy exist (13–15), until recently there have not been specific recommendations for children age <12 years (16,17). As a result, significant practice variation exists. In this issue of the *Journal*, Vasilescu et al. (18) begin to address these gaps by utilizing a countrywide cohort from Finland to comprehensively investigate the genetic etiology of early-onset cardiomyopathy. This represents an important effort to systematically evaluate the molecular basis of disease in a young cohort. Spanning from 1993 to 2014, this cohort consists of children age <15 years who required inotropic support, invasive monitoring, or transplant evaluation. The authors estimate that this represents approximately 40% of the children with cardiomyopathy in Finland. All patients had genetic testing using next-generation sequencing panels of either 101 genes or 117 genes, or whole exome sequencing, with 10 patients having more than 1 test. Overall, molecular diagnoses were made in 39% of the cohort, a higher diagnostic yield than is typically identified in cohorts comprised of diverse cardiomyopathy phenotypes. A strength of the study included the excellent phenotyping in both affected individuals and family members.

Given the rarity of cardiomyopathy in young children, the cohort consisted of only 66 patients. The majority of patients had early-onset disease, with 22 presenting in infancy (age <12 months). Interestingly, the rate of genetic diagnoses was lowest in this group at 34%, with increases to 38%, 60%, and 60% at ages 1 to 5, 6 to 10, and 11 to 15 years, respectively. The infants also had the worst outcome as measured by the rate of death and/or transplantation. In part, this may relate to the preponderance of syndromic and metabolic cases in this age range: of 22 patients with systemic disease (one-third of the study cohort), 16 were diagnosed with cardiomyopathy within the first year of life. Although not truly population-based because the study site ascertained the country's most severe cases, these results provide a first glimpse into the underlying genetics in infants with all cardiomyopathy phenotypes. The causative genes identified represent a second important study finding. Genes previously known to cause other cardiac conditions were identified as causative of pediatric cardiomyopathy. For example, a pathogenic variant in *CALM1*, a genetic cause of catecholaminergic polymorphic ventricular tachycardia, caused cardiomyopathy and arrhythmia in 1 patient. Interestingly, genes important for heart development also caused cardiomyopathy in this study, suggesting possible novel mechanisms in infants and young children compared with adults. Finally, there was a high rate of de novo and autosomal recessive disease. This is clearly related to the incidence of RASopathy cases, many of which were caused by de novo variants, and metabolic cases, which are typically inherited in an autosomal recessive manner. Because cardiomyopathy is

typically considered an autosomal dominant disease with guidelines recommending cardiac surveillance in first-degree relatives, this finding illustrates the importance of understanding the underlying etiology not only for patient management, but for family management.

Vasilescu et al. (18) highlight the need for genetic evaluation to be a routine part of the diagnostic algorithm for children with cardiomyopathy. It is interesting to note that a patient with dilated cardiomyopathy and a homozygous pathogenic variant in *NRAP* met Marburg criteria for myocarditis. Similarly, 2 brothers with autosomal recessive disease resulting from variants in *PPA2* each presented with symptoms of viral infection prior to rapid deterioration. The concept that an environmental trigger such as infection could unmask a genetic predisposition to cardiomyopathy and heart failure is not new. Indeed, it is well established that patients with mitochondrial disorders are at risk for rapid cardiac decompensation during routine illnesses (19). Peripartum cardiomyopathy is another example of a disease resulting from the combination of an environmental stressor (pregnancy) and genetic predisposition for cardiomyopathy (e.g., truncating variants in the gene encoding titin) (20). Despite this, it remains routine to forego genetic evaluation in children with a presumptive diagnosis of myocarditis. Because clinical genetic testing for cardiomyopathy is widely available, studies such as the current one that provide data on patients who benefit from testing are important.

Although it presents several novel findings, there are limitations to the current study. As noted, the cohort size is small and underpowered to make genotype-phenotype correlations. In particular, genetic findings that were associated with rapid disease progression compared with those associated with a stable trajectory need further evaluation in larger studies. This was largely a Finnish cohort, and therefore, the results may not be generalizable to other racial and ethnic populations, although no founder mutations were identified. The authors utilized custom gene panels that do not correspond to panel testing available from a commercial testing laboratory. In fact, only one-half of the molecular diagnoses made in this study would have been identified using cardiomyopathy panels that focus on cytoskeletal and sarcomeric genes. This important result indicates that expanding testing to include genes involved in cardiac development, mitogen-activated protein kinase signaling, and metabolism are important steps in the care of pediatric cardiomyopathy patients, especially infants, but larger studies are required to determine whether exome sequencing is the best first-tier test.

Many challenges remain. The current study demonstrates that while shared genetic causes of cardiomyopathy exist in pediatric and adult populations, kids are not just small adults. A strength of the study was a high rate of identification of syndromic cases and evaluation by a geneticist, but in too many centers this expertise is lacking. Recent guidelines concur that infants and children with cardiomyopathy should be evaluated by clinicians with specific expertise in the recognition and testing of syndromic and nonsyndromic presentations (16,17). Thus, there is a need to increase the numbers of geneticists and cardiologists with cardiovascular genetics expertise to improve clinical care (21). There is also a need for larger longitudinal studies that are focused on all patients with cardiomyopathy, not just the most severely affected, to further establish etiologies and to guide evaluation and genetic testing strategies. Standardizing the genetic evaluation and decreasing practice

variation are important care delivery goals. Only once we routinely understand the cause of a child's cardiomyopathy can we begin to understand the environmental and genetic modifiers of disease, important factors that dictate severity and prognosis. Likewise, the hope of developing targeted therapies for pediatric cardiomyopathy patients is predicated on understanding the underlying disease cause. The study by Vasilescu et al. (18) represents an important step forward in identifying causes in children and emphasizing the implications for treatment.

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