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Clinical Issues in the Pediatric Hypertrophic Cardiomyopathies

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Introduction

The round table discussion concerning clinical issues in hypertrophic cardiomyopathy that took place at the International Workshop on Future Research Directions in Primary and Idiopathic Pediatric Cardiomyopathy in Bethesda in 2006 highlighted a number of issues of particular relevance to the care of children with hypertrophic cardiomyopathy. In general, these discussions revolved around those areas in which it is well recognized that we simply have too little meaningful information to permit reliable decisions concerning clinical management. This manuscript is not intended as a comprehensive review of these issues, but simply highlights several of the more important areas of the conversations that took place.

Nomenclature

The phenotypic similarity of the cardiac manifestations of the various forms of hypertrophic cardiomyopathy has unfortunately led many clinicians to assume that the risks and response to therapy are predictable based on cardiac morphology alone, regardless of etiology. As an attempt to overcome this problem, a recent scientific statement sponsored by the American Heart Association proposed limiting the use of the term “hypertrophic cardiomyopathy” to those disorders caused by mutations in genes encoding contractile proteins of the cardiac sarcomere (1). Some of the problems associated with this proposed solution have already been discussed in an article concerning the nomenclature of the cardiomyopathies that was included in the first issue of this three-part series on pediatric cardiomyopathy (2). In particular, convincing the medical community to change the use of a commonly used term that is based on a clinical definition to one that is restricted to a genetically defined subset of these patients is problematic, particularly when so few of these patients have been genotyped. An alternative solution was suggested in that article (2), namely the specification of the subtype of hypertrophic cardiomyopathy, such as sarcomeric hypertrophic cardiomyopathy or Noonan syndrome-associated hypertrophic cardiomyopathy, which accomplishes a similar goal. Nonetheless, the issue identified here is real and has resulted in discussions and publications that inappropriately fail to distinguish among the various subtypes of hypertrophic cardiomyopathy. Since the outcomes and therefore the appropriate therapy varies according to subtype of hypertrophic cardiomyopathy, failure to distinguish amongst these subtypes can result in dissemination of misinformation and ultimately in mismanagement. For example, early articles on hypertrophic cardiomyopathy in infants reported a 50% survival to age 2 years, leading some centers to recommend transplantation for very young patients with severe hypertrophic cardiomyopathy. When patients with sarcomeric cardiomyopathy are

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distinguished from those with inborn errors of metabolism or mitochondrial disorders, it becomes apparent that survival for those with sarcomeric hypertrophic cardiomyopathy is far better than can be expected with transplantation, whereas those with metabolic disorders are often more impaired by systemic manifestations than by cardiac disability and therefore derive no survival benefit from cardiac transplantation.

Etiology

Pediatric patients in particular manifest the clinical pattern of hypertrophic cardiomyopathy in association with a diverse set of diseases that may have exclusively cardiac manifestations or may involve multiple organ systems. The frequency with which the etiology is defined is quite low, with 75% of children followed in the Pediatric Cardiomyopathy Registry with hypertrophic cardiomyopathy being classified as idiopathic (3). An important impediment to etiologic diagnosis in pediatric hypertrophic cardiomyopathy is the large number of rare diseases that may be responsible. Although new methods for laboratory diagnosis are being developed at an escalating pace, evaluation for many of these rare disorders can be expensive and may be available only through research laboratories. A centralized repository of information concerning laboratories that perform specific testing, the type of biologic specimen required, the costs involved, and the exact procedure for requesting testing is a clinical resource that should be developed.

Genotyping

A large proportion of hypertrophic cardiomyopathy cases in adults are due to sarcomeric gene mutations. Similar data are not available in pediatric hypertrophic cardiomyopathy but it is presumed highly likely that a similar pattern will be seen in older children, although it is possible that infants in particular will manifest a fundamentally different spectrum of mutations. The recent advent of commercially available, CLIA-approved laboratory services for systematic identification of defects in 8 of the 12 sarcomeric genes that have been reported to be responsible for hypertrophic cardiomyopathy (cardiac troponin T, cardiac troponin I, α-tropomyosin, myosin binding protein-C, cardiac myosin heavy chain β, cardiac myosin light chain regulatory, cardiac myosin light chain essential, α-cardiac actin) has made it possible to screen individuals and families. Many concerns have been raised concerning routine genotyping, including expense, implications for insurability, inappropriate delivery of therapy to phenotype-negative gene carriers, and presumptive exclusion from certain activities or professions. Despite initial reluctance, many insurance carriers are now covering this testing and in fact the test is overwhelmingly cost effective if finding the responsible gene in an index case permits identification of even a single genotype-negative child who can therefore be excluded from longitudinal cardiac evaluation. The insurability issue is important but is not unique to hypertrophic cardiomyopathy and this issue must be addressed at a national level if the potential contribution of the genotype-based approach to medicine is ever to succeed. The appropriateness of provision of therapy or exclusion from activities or employment based solely on genotype (4) are issues that can only be addressed once a critical mass of genotype-positive, phenotype-negative individuals have been identified, and, therefore, avoiding genotyping is an inappropriate method of preventing potential missteps with regard to these issues.

There are certainly a number of direct benefits to gene testing, including identification of phenotype-negative individuals who do or do not require routine longitudinal cardiac surveillance, identification of phenotype-negative gene carriers who may benefit from interventions designed to reduce ultimate severity of disease if the gene carrier converts to phenotype-positive, and in occasional instances improved risk-stratification if gene carriage alone, in the absence of detectable phenotypic expression, carries a risk. Although there was

early enthusiasm that genotype might prove more accurate than phenotype for predicting outcome, this expectation has generally not held up under further scrutiny. Nevertheless, there is a small subset of mutations that do represent a particularly high risk independent of phenotype (5).

In addition to the potential direct benefits to individuals and families who undergo genotyping, the availability of a large pool of genotyped children would have important implications. At present, the fact that most instances of hypertrophic cardiomyopathy do not manifest until adulthood has led to speculation that particular mutations (6) or multiple mutations (gene dose effect (7)) might be the cause of early onset of disease. Although hypertrophic cardiomyopathy is reported to be the most common cause of sudden death in young adults and trained athletes (8), it remains unknown whether there is a unique distribution of genotype in these individuals. Furthermore, although the eight sarcomeric genes for which comprehensive screening is available are believed to account for 70% of hypertrophic cardiomyopathy in adults (9), similar data do not exist in children. The argument has been put forward that longitudinal natural history studies are the next reasonable step in genotype-phenotype translational genomics in hypertrophic cardiomyopathy (10). Unless systematic genotyping of children with hypertrophic cardiomyopathy is undertaken, children will be excluded from participation in such longitudinal studies.

Therapy

Current management of children with hypertrophic cardiomyopathy is based nearly exclusively on the experience in adults with familial or sarcomeric hypertrophic cardiomyopathy. Even the recommendations for management in adults are not supported by clinical trials, but instead derive from retrospective reviews and some registry data. It is also widely understood that clinical trials are an unlikely solution. For example, although a randomized trial of implantable cardioverter-defibrillator devices seems a rational solution to determining which hypertrophic cardiomyopathy patients do or do not benefit from their use, the slow pace at which patients achieve hard endpoints, the absence of validated surrogate endpoints, and the absence of therapeutic equipoise in the clinical community virtually dooms such a project. This is a common situation for rare diseases and some seemingly not so rare diseases (11;12). This is also a context in which clinical registries have been particularly helpful. Although it is well documented that recognized and unrecognized sources of bias are far more likely to limit the validity of conclusions drawn from data registries, a well-designed registry can often verify large effect phenomena even though smaller effect phenomena remain of questionable accuracy. The increasingly wide recognition of the futility of attempting to apply the standard randomized clinical trial model to rare diseases has resulted in a higher level of support from the National Institutes of Health for registries for rare diseases (such as the Pediatric Cardiomyopathy Registry) and devices (such as the pediatric ventricular assist device registry). Expansion of these activities appears to offer the best hope to address issues concerning the effectiveness of the various therapies that are currently being used in hypertrophic cardiomyopathy.

Regardless of whether a clinical trial or a registry approach is taken, the lack of information concerning etiology in the pediatric hypertrophic cardiomyopathy is a severe impediment to progress. It is likely that treatment effective in a subset of the population will be missed because of dilution of the study population by patients with quite different diseases. For example, there is no reason to believe that both sarcomeric hypertrophic cardiomyopathy and Noonan syndrome-associated hypertrophic cardiomyopathy would respond similarly to therapy. Etiology-specific therapy is gaining some ground in the diseases associated with inborn errors of metabolism but has yet to impact on the other forms of hypertrophic cardiomyopathy, at least in part because the genotype data are available in too few patients to permit any meaningful

analysis. Progress in this regard will require that the registry approach be paired with a more aggressive approach to genotype identification.

Conclusions

The gaps in our information base for children with hypertrophic cardiomyopathy are large and readily identified. Methods by which to address these shortcomings are more difficult to come by. Several recommendations were forthcoming from the group discussion. 1) The pediatric cardiology community should be encouraged to pursue etiologic diagnosis more vigorously. A centralized listing of commercial and research laboratories offering appropriate testing would facilitate this process. 2) Routine genotyping of children with hypertrophic cardiomyopathy is recommended. 3) Expansion of centralized registries of patients, and therapies such as defibrillator implantation, offer the best practical approach to improving our understanding of these rare disorders.

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